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NEWS	4	Feb 16	TOXLINE no longer being updated
NEWS	5	Apr 23	Search Derwent WPINDEX by chemical structure
NEWS	6	Apr 23	PRE-1967 REFERENCES NOW SEARCHABLE IN CAPLUS AND CA
NEWS	7	May 07	DGENE Reload
NEWS	8	Jun 20	Published patent applications (A1) are now in USPATFULL
NEWS	9	JUL 13	New SDI alert frequency now available in Derwent's DWPI and DPCI

NEWS EXPRESS	August 15 CURRENT WINDOWS VERSION IS V6.0c, CURRENT MACINTOSH VERSION IS V6.0 (ENG) AND V6.0J (JP), AND CURRENT DISCOVER FILE IS DATED 07 AUGUST 2001
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FILE 'HOME' ENTERED AT 16:43:26 ON 21 AUG 2001

=> file embase medline biosis uspatfull japio wpids caplus agricola lifesci biotechds jicst-eplus

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COPYRIGHT (C) 2001 Japan Science and Technology Corporation (JST)

=> e leonard john/au

E1            5     LEONARD JOEL I/AU
E2            1     LEONARD JOHANES/AU
E3           94 --> LEONARD JOHN/AU
E4            5     LEONARD JOHN A/AU
E5            2     LEONARD JOHN B/AU
E6            3     LEONARD JOHN B JR/AU
E7            1     LEONARD JOHN BURTON/AU
E8            1     LEONARD JOHN BURTON JR/AU
E9            3     LEONARD JOHN C/AU
E10           1     LEONARD JOHN CHARLES/AU
E11           1     LEONARD JOHN D/AU
E12           1     LEONARD JOHN D II/AU

=> s e3

L1           94 "LEONARD JOHN"/AU

=> e goldman samuel/au

E1            1     GOLDMAN S Y U/AU
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E3           11 --> GOLDMAN SAMUEL/AU
E4            6     GOLDMAN SAMUEL C/AU
E5            1     GOLDMAN SAMUEL D/AU
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E8            1     GOLDMAN SAMUEL L/AU
E9            5     GOLDMAN SAMUEL M/AU
E10           1     GOLDMAN SANDY/AU
E11           6     GOLDMAN SARAH/AU
E12           2     GOLDMAN SARAH A/AU

=> s e1-e9

L2           78 ("GOLDMAN S Y U"/AU OR "GOLDMAN S Z"/AU OR "GOLDMAN SAMUEL"/AU
                OR "GOLDMAN SAMUEL C"/AU OR "GOLDMAN SAMUEL D"/AU OR "GOLDMAN
                SAMUEL J"/AU OR "GOLDMAN SAMUEL JAY"/AU OR "GOLDMAN SAMUEL
L"/AU
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                OR "GOLDMAN SAMUEL M"/AU)

=> e ohara richard/au

E1          35     OHARA REIKO/AU
E2           1     OHARA RETUKO/AU
E3           0 --> OHARA RICHARD/AU
E4           3     OHARA RIE/AU
E5           5     OHARA RIEKO/AU
E6          91     OHARA RIICHIRO/AU
E7           1     OHARA RIKURO/AU
E8           2     OHARA RISA/AU
E9           2     OHARA RUMIKO/AU
E10          3     OHARA RURI/AU
E11          4     OHARA RURIKO/AU
E12          2     OHARA RYO/AU

=> e o'hara richard/au

MISMATCHED QUOTE IN EXPAND TERM
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MISMATCHED QUOTE IN EXPAND TERM
MISMATCHED QUOTE IN EXPAND TERM
Quotation marks (or apostrophes) must be used in pairs,
one before and one after the expression you are setting
off or masking.

=> e o hara richard/au

E1           3     O HARA RAYMOND J/AU
E2           1     O HARA RAYMOND K/AU
E3           1 --> O HARA RICHARD/AU
E4           1     O HARA RICHARD J/AU
E5           1     O HARA RICHARD JR/AU
E6           1     O HARA RICHARD K/AU
E7          21     O HARA RICHARD M JR/AU
E8           2     O HARA ROBERT/AU
E9           2     O HARA ROBERT B/AU
E10          1     O HARA ROBERT D/AU
E11         26     O HARA ROBERT J/AU
E12          1     O HARA ROBERT M/AU

=> s e3-e7

L3          25 ("O HARA RICHARD"/AU OR "O HARA RICHARD J"/AU OR "O HARA
RICHARD
                JR"/AU OR "O HARA RICHARD K"/AU OR "O HARA RICHARD M JR"/AU)

=> s l1-l3

L4         195 (L1 OR L2 OR L3)

=> s l4 and multiple sclerosis

L5           7 L4 AND MULTIPLE SCLEROSIS

=> dup rem l5
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PROCESSING COMPLETED FOR L5
L6 6 DUP REM L5 (1 DUPLICATE REMOVED)

=> d bib ab 1-6

L6 ANSWER 1 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2001:262593 BIOSIS
DN PREV200100262593
TI Rapamycin inhibits adoptive transfer and prevents relapses in experimental autoimmune encephalomyelitis.
AU Senices, Mayra (1); Dussault, Nancy (1); Harding, Kimberly (1); Sobel, Raymond; **O'Hara, Richard M., Jr. (1)**; Collins, Mary (1); Young, Deborah (1)
CS (1) Genetics Institute-Wyeth Ayerst, 87 Cambridge Park Drive, Cambridge, MA, 02140 USA
SO FASEB Journal, (March 8, 2001) Vol. 15, No. 5, pp. A1209. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB Rapamycin, an immunosuppressive drug approved for transplants, was evaluated in the treatment of a relapsing-remitting model of murine experimental autoimmune encephalomyelitis (EAE). Spleen cells, from SJL/J mice immunized with proteolipid protein (PLP) peptide 139-151, were restimulated in culture and transferred into naive mice. Adoptively transferred mice generally exhibit an acute phase of disease at day 10 which lasts about 12 days, followed by recovery and appearance of milder relapses over the next several months. Daily treatment with oral Rapamycin (15mg/kg) or vehicle from day -1 through 24 in mice followed for 4 months after transfer resulted in 100% EAE incidence in vehicle-fed mice, (mean highest disease score = 1.8 with significant relapse on day 80) and only 10% incidence occurring on day 38 in Rapamycin-fed mice (mean score=1, no relapses). Histologically, Rapamycin treated mice contained significantly lower numbers of inflammatory foci (19 +- 20) compared with controls (167 +- 20). When administered for 20 days at disease onset, Rapamycin improved survival (24/29) over vehicle controls (11/32). Oral rapamycin on an every other day schedule for 40 days was also effective in reducing clinical disease (mean score = 1.8, treated vs. 3.75, controls). In a direct disease model, mice were immunized with PLP in Complete Freund's Adjuvant (CFA) and given Pertussis toxin (ip). In mice treated for 25 days at disease onset, Rapamycin reduced the severity of primary disease when compared with controls, and delayed the occurrence of relapses for 25 days. Our results suggest that Rapamycin prevents the expansion of activated encephalitogenic cells in vivo when given at the time of transfer. At onset of disease, Rapamycin reduces severity and prevents relapses and may therefore be an effective treatment for relapsing forms of **Multiple Sclerosis**.

L6 ANSWER 2 OF 6 USPATFULL
AN 2000:74115 USPATFULL
TI Polynucleotides encoding human CTLA-8 related proteins
IN Jacobs, Kenneth, Newton, MA, United States
Kelleher, Kerry, Marlborough, MA, United States
Carlin, McKeough, Cambridge, MA, United States
Goldman, Samuel, Acton, MA, United States
Pittman, Debra, Windham, NH, United States
Mi, Sha, Belmont, MA, United States

Neben, Steven, Acton, MA, United States
Giannotti, Joanne, Acton, MA, United States
Golden-Fleet, Margaret M., Medford, MA, United States
PA Genetics Institute, Inc., Cambridge, MA, United States (U.S. corporation)
PI US 6074849 20000613
AI US 1996-685239 19960718 (8)
RLI Continuation-in-part of Ser. No. US 1995-514014, filed on 11 Aug 1995
DT Utility
FS Granted
EXNAM Primary Examiner: Draper, Garnette D.
LREP Brown, Scott A., Sprunger, Suzanne A., DesRosier, Thomas J.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1658
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Polynucleotides encoding human CTLA-8 related proteins are disclosed. Human CTLA-8 proteins and methods for their production are also disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8 proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L6 ANSWER 3 OF 6 USPATFULL
AN 2000:37900 USPATFULL
TI Human CTLA-8 and uses of CTLA-8-related proteins
IN Jacobs, Kenneth, Newton, MA, United States
Kelleher, Kerry, Marlborough, MA, United States
Carlin, McKeough, Cambridge, MA, United States
Goldman, Samuel, Acton, MA, United States
Pittman, Debra, Windham, NH, United States
Mi, Sha, Belmont, MA, United States
Neben, Steven, Acton, MA, United States
Giannotti, Joanne, Acton, MA, United States
Golden-Fleet, Margaret M., Medford, MA, United States
PA Genetics Institute, Inc., Cambridge, MA, United States (U.S. corporation)
PI US 6043344 20000328
AI US 1998-34810 19980304 (9)
RLI Division of Ser. No. US 1996-685239, filed on 18 Jul 1996, now abandoned
which is a continuation-in-part of Ser. No. US 1995-504032, filed on 19 Jul 1995 which is a continuation-in-part of Ser. No. US 1995-514014, filed on 11 Aug 1995, now patented, Pat. No. US 5707829
PRAI US 1995-35347 19950719 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Draper, Garnette D.
LREP Lahive & Cockfield, LLP, Mandragouras, Esq., Amy E., Lauro, Esq., Peter C.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1761
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Polynucleotides encoding human CTLA-8 and related proteins are disclosed. Human CTLA-8 proteins and methods for their production are also disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8 proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L6 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 2000:573837 CAPLUS
DN 133:191991
TI Humanized immunoglobulin reactive with B7 molecules and methods of treatment therewith

IN Co, Man Sung; Vasquez, Maximiliano; Carreno, Beatriz; Celniker, Abbie Cheryl; Collins, Mary; **Goldman, Samuel**; Gray, Gary S.; Knight, Andrea; O'Hara, Denise; Rup, Bonita; Veldman, Geertruida M.
PA Genetics Institute, Inc., USA
SO PCT Int. Appl., 162 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000047625	A2	20000817	WO 2000-US3303	20000209

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRAI US 1999-249011 A 19990212
US 1999-339596 A2 19990624
AB The invention relates to humanized anti-B7-2 and anti-B7-1 antibodies, wherein each comprise a variable region of non-human origin and at least a portion of an Ig of human origin. The invention also pertains to methods of treatment for various autoimmune diseases, transplant rejection, inflammatory disorders and infectious diseases by administering humanized anti-B7-2 and/or anti-B7-1 antibodies.

L6 ANSWER 5 OF 6 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
AN 1998:55862 BIOSIS
DN PREV199800055862
TI Regulation of the inflammatory response in animal models of **multiple sclerosis** by interleukin-12.
AU Leonard, John P. (1); Waldburger, Kristine E. (1); Schaub, Robert G. (1); Smith, Terence; Hewson, Adrian K.; Cuzner, M. Louis; **Goldman, Samuel J. (1)**
CS (1) Genetics Inst. Preclinical Pharmacology, Andover, MA 01810 USA
SO Critical Reviews in Immunology, (1997) Vol. 17, No. 5-6, pp. 545-553.
ISSN: 1040-8401.
DT General Review
LA English

L6 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS
AN 1995:934127 CAPLUS
DN 123:337469
TI Use of IL-12 and IL-12 antagonists in treatment of autoimmune diseases
IN Leonard, John P.; **Goldman, Samuel**; **O'Hara, Richard, Jr.**
PA Genetics Institute, Inc., USA
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9524918	A1	19950921	WO 1995-US2550	19950307

W: AU, CA, JP
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

ZA 9500960	A	19951010	ZA 1995-960	19950207
IL 112677	A1	20000131	IL 1995-112677	19950216
CA 2185565	AA	19950921	CA 1995-2185565	19950307
AU 9519749	A1	19951003	AU 1995-19749	19950307

AU 689236 B2 19980326
EP 750509 A1 19970102 EP 1995-912666 19950307
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 09510444 T2 19971021 JP 1995-524044 19950307
PRAI US 1994-212629 A 19940314
WO 1995-US2550 W 19950307
AB Autoimmune conditions such as **multiple sclerosis**, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin-dependent diabetes mellitus, and autoimmune inflammatory eye disease, esp. conditions which are promoted by an increase in levels of IFN-.gamma. or TNF-.alpha., are treated in mammals by administering IL-12 or an IL-12 antagonist. Thus, lymphocytes from mice immunized with myelin proteolipid protein, and restimulated with a synthetic peptide from this protein, were injected into naive mice. The injected mice developed exptl. allergic encephalomyelitis which was exacerbated by incubation of these lymphocytes with IL-12 during restimulation, and alleviated by injection of a polyclonal antibody to IL-12.

=> d clm 2 3

L6 ANSWER 2 OF 6 USPATFULL
CLM What is claimed is:

1. An isolated polynucleotide comprising a nucleotide sequence selected from the group consisting of: (a) the nucleotide sequence of SEQ ID NO:1 from nucleotide 146 to nucleotide 544; and (b) a nucleotide sequence varying from the sequence of the nucleotide sequence specified in (a) as a result of degeneracy of the genetic code.

2. The polynucleotide of claim 1 wherein said nucleotide sequence is operably linked to an expression control sequence.

3. The polynucleotide of claim 1 comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 55 to nucleotide 544.

4. The polynucleotide of claim 1 comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 86 to nucleotide 544.

5. The polynucleotide of claim 2 wherein said polynucleotide is contained in a vector suitable for in vivo expression in a mammalian subject.

6. The polynucleotide of claim 1 comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 139 to nucleotide 544.

7. The polynucleotide of claim 1 comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 146 to nucleotide 544.

8. A host cell transformed with the polynucleotide of claim 2.

9. The host cell of claim 8, wherein said cell is a mammalian cell.

10. A process for producing a human CTLA-8 protein, said process comprising: (a) growing a culture of the host cell of claim 8 in a suitable culture medium; and (b) purifying the human CTLA-8 protein from the culture.

L6 ANSWER 3 OF 6 USPATFULL

CLM What is claimed is:

1. An isolated human CTLA-8 protein comprising an amino acid sequence selected from the group consisting of: (a) the amino acid of SEQ ID NO:2; (b) the amino acid sequence of SEQ ID NO:2 from amino acids 11 to 163; (c) the amino acid sequence of SEQ ID NO:2 from amino acids 29 to 163; (d) the amino acid sequence of SEQ ID NO:2 from amino acids 31 to 163; (e) a fragment of SEQ ID NO:2, the fragment comprising amino acids 11-163 of SEQ ID NO:2; (f) a fragment of SEQ ID NO:2, and the fragment comprising amino acids 29-163 of SEQ ID NO:2; (g) a fragment of SEQ ID NO:2, the fragment comprising amino acids 31-163 of SEQ ID NO:2.

2. The protein of claim 1 comprising the amino acid sequence of SEQ ID NO:2.

3. The protein of claim 1 comprising the sequence from amino acid 29 to 163 of SEQ ID NO:2.

4. The protein of claim 1 comprising the sequence from amino acid 11 to 163 of SEQ ID NO:2.

5. The protein of claim 1 comprising a fragment of SEQ ID NO:2, the fragment comprising amino acids 11-163 of SEQ ID NO:2.

6. The protein of claim 1 comprising a fragment of SEQ ID NO:2, the fragment comprising amino acids 29-163 of SEQ ID NO:2.

7. The protein of claim 1 comprising a fragment of SEQ ID NO:2, the fragment comprising amino acids 31-163 of SEQ ID NO:2.

8. A human CTLA-8 protein produced according to a process which comprises the steps of: (a) growing a culture of a cell in a suitable culture medium, wherein the cell is transformed with a polynucleotide operably linked to an expression control sequence, wherein the polynucleotide is selected from the group consisting of: (aa) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 55 to nucleotide 544; (ab) a polynucleotide comprising the nucleotide sequence of SEQ ID NO:1 from nucleotide 146 to nucleotide 544; (ac) a polynucleotide comprising the nucleotide sequence of the full-length protein coding sequence of clone B18 deposited under accession number ATCC 69868; (ad) a polynucleotide encoding the fill length protein encoded by the cDNA insert of clone B18 deposited under accession number ATCC 69868; and (ae) a polynucleotide comprising a nucleotide sequence varying from the sequence of the nucleotide sequence specified in (aa)-(ad) as a result of degeneracy of the genetic code; and (b) purifying the human CTLA-8 protein encoded by said polynucleotide from the culture.

9. The human CTLA-8 protein of claim 8, wherein said polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 55 to nucleotide 544.

10. The human CTLA-8 protein of claim 8 wherein said polynucleotide comprises the nucleotide sequence of SEQ ID NO:1 from nucleotide 146 to nucleotide 544.

11. The human CTLA-8 protein of claim 8, wherein said polynucleotide comprises the nucleotide sequence of the full-length protein coding sequence of clone B18 deposited under accession number ATCC 69868.

12. The human CTLA-8 protein of claim 8, wherein said polynucleotide comprises a polynucleotide encoding the full length protein encoded by the cDNA insert of clone B18 deposited under accession number ATCC 69868.

13. A pharmaceutical composition comprising a human CTLA-8 protein of claim 1 and a pharmaceutically acceptable carrier.

=> d his

(FILE 'HOME' ENTERED AT 16:43:26 ON 21 AUG 2001)

FILE 'EMBASE, MEDLINE, BIOSIS, USPATFULL, JAPIO, WPIDS, CAPLUS, AGRICOLA,
LIFESCI, BIOTECHDS, JICST-EPLUS' ENTERED AT 16:43:33 ON 21 AUG 2001

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                E LEONARD JOHN/AU
L1           94 S E3
                E GOLDMAN SAMUEL/AU
L2           78 S E1-E9
                E OHARA RICHARD/AU
                E O HARA RICHARD/AU
L3           25 S E3-E7
L4          195 S L1-L3
L5            7 S L4 AND MULTIPLE SCLEROSIS
L6            6 DUP REM L5 (1 DUPLICATE REMOVED)

=> s l4 and (il-12 or interleukin 12 or interlukin)

   7 FILES SEARCHED...
L7           27 L4 AND (IL-12 OR INTERLEUKIN 12 OR INTERLUKIN)

=> s l7 and (antagonist or antibody or antibod?)

L8            9 L7 AND (ANTAGONIST OR ANTIBODY OR ANTIBOD?)

=> dup rem l8

PROCESSING COMPLETED FOR L8
L9            7 DUP REM L8 (2 DUPLICATES REMOVED)

=> d bib ab 1-7

L9   ANSWER 1 OF 7  USPATFULL
AN     2000:74115  USPATFULL
TI     Polynucleotides encoding human CTLA-8 related proteins
IN     Jacobs, Kenneth, Newton, MA, United States
       Kelleher, Kerry, Marlborough, MA, United States
       Carlin, McKeough, Cambridge, MA, United States
       Goldman, Samuel, Acton, MA, United States
       Pittman, Debra, Windham, NH, United States
       Mi, Sha, Belmont, MA, United States
       Neben, Steven, Acton, MA, United States
       Giannotti, Joanne, Acton, MA, United States
       Golden-Fleet, Margaret M., Medford, MA, United States
PA     Genetics Institute, Inc., Cambridge, MA, United States (U.S.
       corporation)
PI     US 6074849              20000613
AI     US 1996-685239          19960718 (8)
RLI    Continuation-in-part of Ser. No. US 1995-514014, filed on 11 Aug 1995
DT     Utility
FS     Granted
EXNAM  Primary Examiner: Draper, Garnette D.
LREP   Brown, Scott A., Sprunger, Suzanne A., DesRosier, Thomas J.
CLMN   Number of Claims: 10
ECL    Exemplary Claim: 1
```

DRWN 10 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1658
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Polynucleotides encoding human CTLA-8 related proteins are disclosed. Human CTLA-8 proteins and methods for their production are also disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8 proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L9 ANSWER 2 OF 7 USPATFULL
AN 2000:37900 USPATFULL
TI Human CTLA-8 and uses of CTLA-8-related proteins
IN Jacobs, Kenneth, Newton, MA, United States
Kelleher, Kerry, Marlborough, MA, United States
Carlin, McKeough, Cambridge, MA, United States
Goldman, Samuel, Acton, MA, United States
Pittman, Debra, Windham, NH, United States
Mi, Sha, Belmont, MA, United States
Neben, Steven, Acton, MA, United States
Giannotti, Joanne, Acton, MA, United States
Golden-Fleet, Margaret M., Medford, MA, United States
PA Genetics Institute, Inc., Cambridge, MA, United States (U.S. corporation)
PI US 6043344 20000328
AI US 1998-34810 19980304 (9)
RLI Division of Ser. No. US 1996-685239, filed on 18 Jul 1996, now abandoned
which is a continuation-in-part of Ser. No. US 1995-504032, filed on 19 Jul 1995 which is a continuation-in-part of Ser. No. US 1995-514014, filed on 11 Aug 1995, now patented, Pat. No. US 5707829
PRAI US 1995-35347 19950719 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Draper, Garnette D.
LREP Lahive & Cockfield, LLP, Mandragouras, Esq., Amy E., Lauro, Esq., Peter C.
CLMN Number of Claims: 13
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1761
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Polynucleotides encoding human CTLA-8 and related proteins are disclosed. Human CTLA-8 proteins and methods for their production are also disclosed. Methods of treatment using human CTLA-8 proteins, rat CTLA-8 proteins and herpesvirus herpes CTLA-8 proteins are also provided.

L9 ANSWER 3 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 1
AN 1998:80243 BIOSIS
DN PREV199800080243
TI Immunoregulation by **interleukin-12** in MB49.1 tumor bearing mice: Cellular and cytokine-mediated effector mechanisms.
AU Hunter, Sharon E.; Waldburger, Kristine E.; Thibodeaux, Deborah K.; Schaub, Robert G.; **Goldman, Samuel J.**; Leonard, John P. (1)
CS (1) Genet. Inst., One Burtt Rd., Andover, MA 01810 USA
SO European Journal of Immunology, (Dec., 1997) Vol. 27, No. 12, pp. 3438-3446.
ISSN: 0014-2980.
DT Article
LA English
AB Administration of recombinant murine interleukin (rmIL)-12 to MB49.1 tumor-bearing mice results in dose-dependent regression of the primary tumor and the generation of protective antitumor immunity in the majority of animals. rmIL-12 administration is associated with a marked increase in
lymph node cellularity that is predominantly due to the expansion of B220+

B cells as well as CD8+ T cells. Stimulation of lymph node cells from rmIL-12-treated, but not control tumor-bearing mice, with MB49.1 tumor cells in vitro was shown to enhance the secretion of interferon (IFN)-gamma. The magnitude of this in vitro response was dependent on the dose of rmIL-1 2 administered in vivo and mirrored the change in circulating serum IFN-gamma. Furthermore, at the height of the in vitro response to tumor stimulation, the addition of a neutralizing **antibody** to murine **IL-12** suppressed IFN-gamma production, indicating a role for endogenous **IL-12** in this antigen-specific cytokine response. Although studies in SCID mice confirmed that an appropriate T cell response was required for rmIL-12-mediated antitumor activity, in immunocompetent animals early tumor regression was not accompanied by cellular infiltration of the tumor. In contrast, a profound increase in tumor-associated inducible nitric oxide synthase (iNOS) was observed in mice receiving rmIL-12 which preceded T cell infiltration of the tumor which could be detected during the second week of **IL-12** treatment. Direct tumor killing through the cytotoxic actions of NO via the iNOS pathway may serve as a way of generating tumor antigen which enables the host to mount a subsequent T cell response against the tumor.

L9 ANSWER 4 OF 7 CAPLUS COPYRIGHT 2001 ACS
AN 1998:12658 CAPLUS
DN 128:87479
TI Regulation of the inflammatory response in animal models of multiple sclerosis by **interleukin-12**
AU Leonard, John P.; Waldburger, Kristine E.; Schaub, Robert G.; Smith, Terence; Hewson, Adrian K.; Cuzner, M. Louise; **Goldman, Samuel J.**
CS Genetics Institute, Preclinical Pharmacology, Andover, MA, 01810, USA
SO Crit. Rev. Immunol. (1997), 17(5 & 6), 545-553
CODEN: CCRIDE; ISSN: 1040-8401
PB Begell House, Inc.
DT Journal; General Review
LA English
AB A review with 54 refs. **Interleukin 12** (**IL-12**), a novel heterodimeric protein produced primarily by antigen-presenting cells, serves as a key regulator of innate and adaptive immune responses. In addn. to being a potent inducer of IFN-.gamma., **IL-12** is widely considered to be the principal cytokine that regulates the generation of Th1 type effector cells. As the successful induction of exptl. autoimmune encephalomyelitis (EAE) is assocd. with a strong Th1 type cellular response, we have evaluated the role of **IL-12** in regulating the pathogenesis of EAE in SJL/J mice and Lewis rats. In both settings, treatment with **IL-12** was found to accelerate the onset and increase the severity and duration of clin. disease. More importantly, administration of **IL-12** to Lewis rats that had recovered from primary disease was found to trigger clin. relapse. In all instances, **IL-12**-induced exacerbation was assocd. with a profound increase in iNOS pos. macrophages within the perivascular lesions. Although **IL-12**-induced IFN-.gamma. does not appear to be required for exacerbation of disease, neutralizing **antibodies** against murine **IL-12** delay the onset and reduce the severity of adoptively transferred EAE, indicating a role for endogenous **IL-12** as regulator of disease. Based on the above findings, effective inhibition of **IL-12** in vivo may have great therapeutic value in the treatment of MS and other Th1-assocd. inflammatory disorders.

L9 ANSWER 5 OF 7 CAPLUS COPYRIGHT 2001 ACS
AN 1997:285388 CAPLUS
DN 126:329093
TI Effects of **interleukin 12** on hematopoietic stem and

progenitor cells
AU Neben, Steven; **Leonard, John; Goldman, Samuel;** Ploemacher, Rob E.
CS Department of Immunology and Hematopoiesis, Genetics Institute, Inc., Cambridge, MA, USA
SO Bone Marrow Transplant.: Basic Clin. Stud., [Pap. Int. Symp. BMT] (1996), Meeting Date 1995, 28-35. Editor(s): Ikehara, Susumu; Takaku, Fumimaro; Good, Robert A. Publisher: Springer, Tokyo, Japan.
CODEN: 64HVAW
DT Conference; General Review
LA English
AB A review with 34 refs. **Interleukin-12** (**IL-12**) has been shown to possess potent immunomodulatory activity. It has a unique structure among cytokines, consisting of two covalently linked subunits, one with homol. to other members of the cytokine superfamily, the other being highly homologous to gp130, the signaling subunit of a no. of cytokine receptors. Here we summarize studies showing that **IL-12** is a hematopoietic growth factor with potent activity on hematopoietic stem and progenitor cells. In clonal and liq. culture assays, **IL-12** synergizes with IL-3 and Steel Factor to increase the no. of colonies as well as to expand both stem and progenitor cell content in the cultures. In stroma-dependent long-term bone marrow cultures, **IL-12** addn. causes a decrease in cell prodn. in the first week after inoculation of whole bone marrow cells, followed by an increase in both mature cells and progenitor cells over the next 3 wk. The initial decrease appears to be mediated by **IL-12**-induced prodn. of IFN-.gamma., possibly by natural killer cells and/or T cells which do not persist in these cultures. Studies in naive mice demonstrate a similar acute decrease in peripheral leukocyte count, mediated by IFN-.gamma., upon administration of **IL-12**. In contrast, despite a significant decrease in peripheral platelet count, reticulated platelets become elevated and mean megakaryocyte ploidy in the bone marrow shifts from 16N to 32N during **IL-12** treatment. These **IL-12**-mediated effects on megakaryopoiesis are abrogated by simultaneous treatment of mice with **antibodies** against IFN-.gamma.. These studies provide further information on the potential physiol. role and applications of **IL-12** outside the immune system.

L9 ANSWER 6 OF 7 CAPLUS COPYRIGHT 2001 ACS
AN 1995:934127 CAPLUS
DN 123:337469
TI Use of **IL-12** and **IL-12** antagonists in treatment of autoimmune diseases
IN Leonard, John P.; **Goldman, Samuel; O'Hara, Richard, Jr.**
PA Genetics Institute, Inc., USA
SO PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9524918	A1	19950921	WO 1995-US2550	19950307
	W: AU, CA, JP				
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
	ZA 9500960	A	19951010	ZA 1995-960	19950207
	IL 112677	A1	20000131	IL 1995-112677	19950216
	CA 2185565	AA	19950921	CA 1995-2185565	19950307
	AU 9519749	A1	19951003	AU 1995-19749	19950307
	AU 689236	B2	19980326		
	EP 750509	A1	19970102	EP 1995-912666	19950307
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

JP 09510444 T2 19971021 JP 1995-524044 19950307
PRAI US 1994-212629 A 19940314
WO 1995-US2550 W 19950307
AB Autoimmune conditions such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, autoimmune pulmonary inflammation, Guillain-Barre syndrome, autoimmune thyroiditis, insulin-dependent diabetes mellitus, and autoimmune inflammatory eye disease, esp. conditions which are promoted by an increase in levels of IFN-.gamma. or TNF-.alpha., are treated in mammals by administering **IL-12** or an **IL-12 antagonist**. Thus, lymphocytes from mice immunized with myelin proteolipid protein, and restimulated with a synthetic peptide from this protein, were injected into naive mice. The injected mice developed exptl. allergic encephalomyelitis which was exacerbated by incubation of these lymphocytes with **IL-12** during restimulation, and alleviated by injection of a polyclonal **antibody** to **IL-12**.

L9 ANSWER 7 OF 7 BIOSIS COPYRIGHT 2001 BIOSIS DUPLICATE 2
AN 1993:343704 BIOSIS
DN PREV199396040704
TI Resolution of cutaneous leishmaniasis: **Interleukin 12** initiates a protective T helper type 1 immune response.
AU Sypek, Joseph P. (1); Chung, Charles L.; Mayor, Sharon E. H.; Subramanyam, Janaki M.; **Goldman, Samuel L.**; Sieburth, Derek S.; Wolf, Stanley F.; Schaub, Robert G.
CS (1) Dep. Preclin. Biol., Genetics Inst. Inc., 87 Cambridge Park Dr., Cambridge, MA 02140 USA
SO Journal of Experimental Medicine, (1993) Vol. 177, No. 6, pp. 1797-1802. ISSN: 0022-1007.
DT Article
LA English
AB Resistance to Leishmania major in mice is associated with the appearance of distinct T helper type 1 (Th1) and Th2 subsets. T cells from lymph nodes draining cutaneous lesions of resistant mice are primarily interferon y (IFN-gamma)-producing Th1 cells. In contrast, T cells from susceptible mice are principally Th2 cells that generate interleukin 4 (IL-4). Although existing evidence is supportive of a role for IFN-gamma in the generation of Th1 cells, additional factors may be required for a protective response to be maintained. A potential candidate is **IL-12**, a heterodimeric cytokine produced by monocytes and B cells that has multiple effects on T and natural killer cell function, including inducing IFN-gamma production. Using an experimental leishmanial model we have observed that daily intraperitoneal administration at the time of parasite challenge of either 0.33 mu-g **IL-12** (a consecutive 5 d/wk for 5 wk) or 1.0 mu-g **IL-12** per mouse (only a consecutive 5 d) caused a gt 75% reduction in parasite burden at the site of infection, in highly susceptible BALB/c mice. Delay of treatment by 1 wk had less of a protective effect. Concomitant with these protective effects was an increase in IFN-gamma and a decrease in IL-4 production, as measured by enzyme-linked immunosorbent assay of supernatants generated from popliteal lymph node cells stimulated with leishmanial antigen in vitro. The reduction in parasite numbers induced by **IL-12** therapy was still apparent at 10 wk postinfection. In addition, we observed that the administration of a rabbit anti-recombinant murine **IL-12** polyclonal **antibody** (200 mu-g i.p. every other day for 25 d) at the time of infection to resistant C57Bl/6 mice exacerbated disease. These effects were accompanied by a shift in IFN-gamma production in vitro by antigen-stimulated lymph node cells indicative of a Th2-like response. These findings suggest that **IL-12** has an important role in initiating a Th1 response and protective immunity.

=> s IL-12 and multiple sclerosis

L10 609 IL-12 AND MULTIPLE SCLEROSIS

=> s l10 and (antagonist or antibod?)

L11 303 L10 AND (ANTAGONIST OR ANTIBOD?)

=> s l11 and il-12 antibod?

L12 51 L11 AND IL-12 ANTIBOD?

=> dup rem l12

PROCESSING COMPLETED FOR L12
L13 32 DUP REM L12 (19 DUPLICATES REMOVED)

=> d bib ab 1-32

L13 ANSWER 1 OF 32 USPATFULL
AN 2001:116556 USPATFULL
TI Protein kinase homologs
IN Bandman, Olga, Mountain View, CA, United States
Tang, Y. Tom, San Jose, CA, United States
Hillman, Jennifer L., Mountain View, CA, United States
Yue, Henry, Sunnyvale, CA, United States
Guegler, Karl J., Menlo Park, CA, United States
Corley, Neil C., Mountain View, CA, United States
Gorgone, Gina A., Boulder Creek, CA, United States
Azimzai, Yalda, Union City, CA, United States
Lu, Dyung Aina M., San Jose, CA, United States
PA Incyte Genomics, Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 6264947 B1 20010724
AI US 1999-420915 19991020 (9)
RLI Division of Ser. No. US 1998-173581, filed on 15 Oct 1998, now patented,
Pat. No. US 6013455, issued on 11 Jan 2000
DT Utility
FS GRANTED
EXNAM Primary Examiner: Prouty, Rebecca E.; Assistant Examiner: Monshipouri, Maryam
LREP Incyte Genomics, Inc.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 2493
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides human protein kinase homologs (PKH) and polynucleotides which identify and encode PKH. The invention also provides expression vectors, host cells, **antibodies**, agonists, and antagonists. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of PKH.

L13 ANSWER 2 OF 32 USPATFULL
AN 2001:108030 USPATFULL
TI Inhibitors of Interleukin-1.beta. converting enzyme
IN Batchelor, Mark James, Cumnor Hill, United Kingdom
Bebbington, David, Pewsey, United Kingdom
Bemis, Guy W., Arlington, MA, United States
Fridman, Wolf Herman, Paris, France
Gillespie, Roger John, Oaksey, United Kingdom
Golec, Julian M. C., Ashbury, United Kingdom

Gu, Yong, Brookline, MA, United States
Lauffer, David J., Stow, MA, United States
Livingston, David J., Newtonville, MA, United States
Matharu, Saroop Singh, Cricklade, United Kingdom
Mullican, Michael D., Needham, MA, United States
Murcko, Mark A., Holliston, MA, United States
Murdoch, Robert, Highworth, United Kingdom
Nyce, Philip, Milbury, MA, United States
Robidoux, Andrea L. C., Andover, MA, United States
Su, Michael, Newton, MA, United States
Wannamaker, M. Woods, Stow, MA, United States
Wilson, Keith P., Hopkinton, MA, United States
Zelle, Robert E., Stow, MA, United States
PA Vertex Pharmaceuticals, Incorporated, Cambridge, MA, United States (U.S. corporation)
PI US 6258948 B1 20010710
AI US 1999-400639 19990921 (9)
RLI Division of Ser. No. US 1996-761483, filed on 6 Dec 1996 Continuation-in-part of Ser. No. US 1996-712878, filed on 12 Sep 1996, now patented, Pat. No. US 5985863 Continuation-in-part of Ser. No. US 1996-598332, filed on 8 Feb 1996, now patented, Pat. No. US 5874424 Continuation-in-part of Ser. No. US 1995-575641, filed on 20 Dec 1995, now patented, Pat. No. US 6008217
PRAI US 1996-31495 19961126 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Kifle, Bruck
LREP Fish & Neave, Haley, Jr., Esq., James F., Joslyn, Kristin M.
CLMN Number of Claims: 46
ECL Exemplary Claim: 1
DRWN 21 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 13229
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel classes of compounds which are inhibitors of interleukin-IB converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against IL-1-, apoptosis-, IGIF-, and IFN-.gamma.-mediated diseases, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, and necrotic diseases. This invention also relates to methods for inhibiting ICE activity, for treating interleukin-1-, apoptosis-, IGIF- and IFN-.gamma.-mediated diseases and decreasing IGIF and IFN-.gamma. production using the compounds and compositions of this invention. This invention also relates to methods for preparing N-acylamino compounds.

L13 ANSWER 3 OF 32 USPATFULL
AN 2001:107647 USPATFULL
TI Human **antibodies** that bind human TNF.alpha.
IN Salfeld, Jochen G., North Grafton, MA, United States
Allen, Deborah J., Cambridge, United Kingdom
Hoogenboom, Hendricus R. J. M., Hertogsingel, MA, United States
Kaymakcalan, Zehra, Westboro, MA, United States
Labkovsky, Boris, Framingham, MA, United States
Mankovich, John A., Andover, MA, United States
McGuinness, Brian T., Comberton, United Kingdom
Roberts, Andrew J., Cambridge, United Kingdom
Sakorafas, Paul, Newton, MA, United States
Schoenhaut, David, Garfield, NJ, United States
Vaughan, Tristan J., Impington, United Kingdom

White, Michael, Framingham, MA, United States
Wilton, Alison J., Cambridge, United Kingdom
PA BASF Aktiengesellschaft, Rheiland-Pfalz, Germany, Federal Republic of (non-U.S. corporation)
PI US 6258562 B1 20010710
WO 9729131 19970814
AI US 1999-125098 19990316 (9)
WO 1997-US2219 19970210
19990316 PCT 371 date
19990316 PCT 102(e) date
RLI Continuation-in-part of Ser. No. US 1996-599226, filed on 9 Feb 1996, now patented, Pat. No. US 6090382
PRAI US 1996-31476 19961125 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Saunders, David
LREP Lahive & Cockfield, LLP, DeConti, Jr., Giulio A., Hanley, Elizabeth A.
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 2754
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Human **antibodies**, preferably recombinant human **antibodies**, that specifically bind to human tumor necrosis factor .alpha.(hTNF.alpha.) are disclosed. These **antibodies** have high affinity for hTNF.alpha. (e.g., K.sub.d =10.sup.-8 M or less), a slow off rate for hTNF.alpha. dissociation (e.g., K.sub.off =10.sup.-3 sec.sup.-1 or less) and neutralize hTNF.alpha. activity in vitro and in vivo. An **antibody** of the invention can be a full-length **antibody** or an antigen-binding portion thereof. The **antibodies**, or **antibody** portions, of the invention are useful for detecting hTNF.alpha. and for inhibiting hTNF.alpha. activity, e.g., in a human subject suffering from a disorder in which hTNF.alpha. activity is detrimental. Nucleic acids, vectors and host cells for expressing the recombinant human **antibodies** of the invention, and methods of synthesizing the recombinant human **antibodies**, are also encompassed by the invention.

L13 ANSWER 4 OF 32 USPATFULL
AN 2001:63494 USPATFULL
TI **Antibodies** against human **IL-12**
IN Gately, Maurice Kent, Parsippany, NJ, United States
Presky, David Howard, Glen Ridge, NJ, United States
PA Hoffman-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 6225117 B1 20010501
AI US 1999-232522 19990119 (9)
PRAI US 1998-72333 19980123 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Chan, Christina Y.; Assistant Examiner: DiBrino, Marianne
LREP Johnston, George W., Rocha-Tramaloni, Patricia S., Silverman, Robert A.
CLMN Number of Claims: 23
ECL Exemplary Claim: 1
DRWN 7 Drawing Figure(s); 7 Drawing Page(s)
LN.CNT 1122
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel p75 heterodimer specific anti-human **IL-12 antibodies** that are characterized by a higher potency and greater efficacy in neutralizing human **IL-12** bioactivity than known heterodimer specific **IL-12** monoclonal **antibodies**. The heterodimer specific **antibodies** recognize one or more epitopes

of the human **IL-12** p75 heterodimer, but do not bind to the p40 subunit alone. The heterodimer specific **IL-12 antibodies** neutralize rhesus monkey **IL-12** bioactivity with a potency similar to their potency for neutralizing human **IL-12** bioactivity making them useful **IL-12** antagonists for in vivo studies in the rhesus monkey.

L13 ANSWER 5 OF 32 USPATFULL
AN 2001:52062 USPATFULL
TI Thienodipyridine derivatives, production and use thereof
IN Sohda, Takashi, Takatsuki, Japan
Makino, Haruhiko, Hyogo, Japan
Baba, Atsuo, Ashiya, Japan
Yamane, Taihei, Ikeda, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6214838 B1 20010410
WO 9965916 19991223
AI US 1999-355218 19990723 (9)
WO 1999-JP3155 19990614
19990723 PCT 371 date
19990723 PCT 102(e) date
PRAI JP 1998-166910 19980615
DT Utility
FS Granted
EXNAM Primary Examiner: Huang, Evelyn Mei
LREP Riesen, Philippe Y., Chao, Mark
CLMN Number of Claims: 33
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1733
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound of the formula (I): ##STR1##

wherein R is hydrogen or C.sub.2-6 alkanoyl; X is halogen; and ring A is

benzene ring which is optionally substituted by 1 to 4 substituents selected from 1 halogen, 2 hydroxy, 3 C.sub.1-6 alkoxy optionally substituted by halogen or phenyl, 4 C.sub.1-6 alkylthio optionally substituted by halogen or phenyl, 5 C.sub.1-6 alkyl optionally substituted by halogen, 6 C.sub.2-6 alkanoylamino or 7 carboxy optionally esterified by C.sub.1-6 alkyl, or a salt thereof; which can be used for preventing or treating inflammatory disease, arthritis, chronic rheumatoid arthritis, autoimmune diseases, or rejection after organ transplantation.

L13 ANSWER 6 OF 32 USPATFULL
AN 2001:40475 USPATFULL
TI Inhibitors of interleukin-1.beta. Converting enzyme inhibitors
IN Batchelor, Mark James, Cumnor Hill, United Kingdom
Bebbington, David, Pewsey, United Kingdom
Bemis, Guy W., Arlington, MA, United States
Fridman, Wolf Herman, Paris, France
Gillespie, Roger John, Malmesbury, United Kingdom
Golec, Julian M. C., Swindon, United Kingdom
Gu, Yong, Brookline, MA, United States
Lauffer, David J., Stow, MA, United States
Livingston, David J., Newtonville, MA, United States
Matharu, Saroop Singh, Cricklade, United Kingdom
Mullican, Michael D., Needham, MA, United States
Murcko, Mark A., Holliston, MA, United States
Murdoch, Robert, Highworth, United Kingdom
Nyce, Philip, Milbury, MA, United States
Robidoux, Andrea L. C., Andover, MA, United States
Su, Michael, Newton, MA, United States

Wannamaker, M. Woods, Stow, MA, United States
Wilson, Keith P., Hopkinton, MA, United States
Zelle, Robert E., Stow, MA, United States
PA Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States (U.S. corporation)
PI US 6204261 B1 20010320
AI US 1996-761483 19961206 (8)
RLI Continuation-in-part of Ser. No. US 1996-712878, filed on 12 Sep 1996 Continuation-in-part of Ser. No. US 1996-598332, filed on 8 Feb 1996, now patented, Pat. No. US 5874424 Continuation-in-part of Ser. No. US 1995-575641, filed on 20 Dec 1995
PRAI US 1996-31495 19961126 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Gupta, Yogendra N.; Assistant Examiner: Kifle, Bruck
LREP Fish & Neave, Haley, Jr., James F., Dixon, Lisa A.
CLMN Number of Claims: 34
ECL Exemplary Claim: 1
DRWN 20 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 12975
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to pyradazino[1,2-a][1,2]diazepine-1-carboxamide compounds of formula: ##STR1##

which compounds are inhibitors of interleukin-1beta converting enzyme.

L13 ANSWER 7 OF 32 USPATFULL
AN 2000:80750 USPATFULL
TI Substituted benzamides
IN Germann, Tieno, Herzogenrath, Germany, Federal Republic of
Frosch, Stefanie, Aachen, Germany, Federal Republic of
Zimmer, Oswald, Wuerselen, Germany, Federal Republic of
PA Gruenenthal GmbH, Aachen, Germany, Federal Republic of (non-U.S. corporation)
PI US 6080742 20000627
AI US 1999-405180 19990924 (9)
PRAI DE 1998-19843793 19980924
DT Utility
FS Granted
EXNAM Primary Examiner: Stockton, Laura L.
LREP Evenson, McKeown, Edwards & Lenahan, P.L.L.C.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 426
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Substituted benzamides corresponding to the formula I ##STR1## wherein R.sup.1, R.sup.2 and R.sup.3 have the meanings given herein, and their use in pharmaceutical compositions. The compounds are particularly useful as immunomodulators.

L13 ANSWER 8 OF 32 USPATFULL
AN 2000:50737 USPATFULL
TI Methods and compositions for modulating responsiveness to corticosteroids
IN Sekut, Les, Westborough, MA, United States
Carter, Adam, Newburyport, MA, United States
Ghayur, Tariq, Grafton, MA, United States
Banerjee, Subhashis, Shrewsbury, MA, United States
Tracey, Daniel E., Harvard, MA, United States
PA BASF Aktiengesellschaft, Rheinland Pfalz, Germany, Federal Republic of (non-U.S. corporation)
PI US 6054487 20000425
AI US 1997-820692 19970318 (8)
DT Utility

FS Granted
EXNAM Primary Examiner: Jarvis, William R. A.
LREP Lahive & Cockfield, LLP
CLMN Number of Claims: 46
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 2404
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Method for modulating responsiveness to corticosteroids in a subject are provided. In the method of the invention, an agent which antagonizes a factor that regulates production of IFN-.gamma. in the subject is administered to the subject in combination with a corticosteroid such that responsiveness of the subject to the corticosteroid is modulated as compared to when a corticosteroid alone is administered to the subject. In one embodiment, the agent is an interferon-.gamma. inducing factor (IGIF) **antagonist**. In another embodiment, the agent is an interleukin-12 (**IL-12**) **antagonist**. In a preferred embodiment, the agent is an inhibitor of a caspase family protease, preferably an ICE inhibitor. In another preferred embodiment, the agent is an anti-**IL-12** monoclonal **antibody**. Other preferred agents include phosphodiesterase IV inhibitors and beta-2 agonists. The methods of the invention can be used in the treatment of a variety of inflammatory and immunological diseases and disorders. Pharmaceutical compositions comprising an agent which antagonizes a factor that regulates production of IFN-.gamma. in a subject, a corticosteroid and a pharmaceutically acceptable carrier are also provided. A preferred composition comprises an ICE inhibitor, a corticosteroid and a pharmaceutically acceptable carrier.

L13 ANSWER 9 OF 32 USPATFULL
AN 2000:4618 USPATFULL
TI Protein kinase homologs
IN Bandman, Olga, Mountain View, CA, United States
Yang, Y. Tom, San Jose, CA, United States
Hillman, Jennifer L., Mountain View, CA, United States
Yue, Henry, Sunnyvale, CA, United States
Guegler, Karl J., Menlo Park, CA, United States
Corley, Neil C., Mountain View, CA, United States
Gorgone, Gina A., Boulder Creek, CA, United States
Azimzai, Yalda, Union City, CA, United States
Lu, Dyung Aina M., San Jose, CA, United States
PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 6013455 20000111
AI US 1998-173581 19981015 (9)
DT Utility
FS Granted
EXNAM Primary Examiner: Achutamurthy, Ponnathapu; Assistant Examiner: Moshipouri, M.
LREP Muenzen, Colette C.Incyte Pharmaceuticals, Inc.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 3258
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides human protein kinase homologs (PKH) and polynucleotides which identify and encode PKH. The invention also provides expression vectors, host cells, **antibodies**, agonists, and antagonists. The invention also provides methods for diagnosing, treating or preventing disorders associated with expression of PKH.

L13 ANSWER 10 OF 32 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2001-102680 [11] WPIDS
DNC C2001-030059
TI New morpholinyl triazine derivatives, useful as interleukin-12 inhibitors for treating e.g. sepsis and autoimmune disorders such as rheumatoid arthritis, Crohn's disease, psoriasis and **multiple sclerosis**.
DC B02 B03
IN BRUNKHORST, B; ONO, M; VO, N H; WADA, Y; WARCHOL, T; WRONA, W; ZHOU, D
PA (SHIO) SHIONOGI BIORESEARCH CORP
CYC 91
PI WO 2000078757 A1 20001228 (200111)* EN 45p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TZ UG ZW
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW
AU 2000056074 A 20010109 (200122)
ADT WO 2000078757 A1 WO 2000-US16094 20000612; AU 2000056074 A AU 2000-56074 20000612
FDT AU 2000056074 A Based on WO 200078757
PRAI US 1999-139623 19990617
AB WO 200078757 A UPAB: 20010224
NOVELTY - Morpholinyl triazine derivatives (I) and their salts are new.
DETAILED DESCRIPTION - Morpholinyl triazine derivatives of formula (I) and their salts are new.
X = triazinyl;
L1 = A1-B1;
A1-= (CH(Ra))m, O, S or N(Rb);
B1 = (CH(Rc))n or a bond;
Ra, Rc = H, alkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, thio, thioalkyl, cyano, nitro, alkylcarbonylamino, alkylaminocarbonyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkylcarbonyloxy, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl;
Rb = H, alkyl, cycloalkyl, heterocycloalkyl, aryl, aralkyl, heteroaryl or heteroaralkyl;
m, n = 1-8;
W = cycloalkyl, heterocycloalkyl, aryl or heteroaryl, all optionally substituted by alkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, thio, thioalkyl, cyano, nitro, alkylcarbonylamino, alkylaminocarbonyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl or alkylcarbonyloxy;
L2 = A2-B2
A2 = a bond, N(R1) or (C(R2)(R3))p;
B2 = a bond, N=C(R4), C(R5)=N, C(R6)=C(R7), N(R8)=N(R9), N(R10)C(R11)(R12), OC(R13)(R14), COC(R15)(R16), CON(R17), N(R18)CO, CO, COO, COS, SC(R19)(R20), CS-C(R21)(R22), CS-N(R23), N(R24)CS, CS or SO2;
or
A2-B2 = O, S, (O(CH2)qO)r, (N(R25)(CH2)sCO)t or (N(R26)(CH2)uN(R27))v;
provided that A2-B2 is not a bond;
R1-R27 = H, alkyl, alkoxy, hydroxyl, hydroxylalkyl, halo, haloalkyl, amino, aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl
or heteroaralkyl;
p, q, r, s, t, u, v =.1-3;
Y = R'-L'-R'';
L' = a bond, O, S, N(R28), N(R29)CO, CON(R30), COO or OCO;
R28-R30 = H, alkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl;
R' = a bond, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl, all optionally substituted by alkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, thio,

thioalkyl, cyano, nitro, alkylcarbonylamino, alkylaminocarbonyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, alkylcarbonyloxy or alkoxycarbonylimino;

R'' = cycloalkyl, heterocycloalkyl, aryl, heteroaryl, aralkyl or heteroaralkyl, all optionally substituted by alkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo, haloalkyl, amino, aminoalkyl, thio, thioalkyl, cyano, nitro, alkylcarbonylamino, alkylaminocarbonyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl, or alkylcarbonyloxy;

Z = morpholinyl optionally substituted by alkyl, alkoxy, hydroxyl, hydroxylalkyl, carboxyl, halo; haloalkyl, amino, aminoalkyl, thio, thioalkyl, cyano, nitro, alkylcarbonylamino, alkylaminocarbonyl, formyl, alkylcarbonyl, alkylcarbonylalkyl, alkoxycarbonyl or alkylcarbonyloxy.

ACTIVITY - Antiinflammatory; antirheumatic; antiarthritic; antipsoriatic; antibacterial; immunosuppressive; neuroprotective.

MECHANISM OF ACTION - Inhibitor of interleukin (**IL**)-**12** production (claimed).

Using mononuclear cells from human peripheral blood (PBMC), a number of tested compounds (I) (unspecified) demonstrated over 70% inhibition of **IL-12** compared to control. In a specificity assay, the 2 most potent compounds (I) (out of 9, all unspecified), exhibited a 10-fold increase in inhibiting **IL-12** production over a known anti-inflammatory compound, dexamethazone.

USE - For inhibiting **IL-12** production or treating **IL-12** mediated disorders including sepsis and autoimmune disorders e.g. rheumatoid arthritis, Crohn's disease, psoriasis and **multiple sclerosis**. Prior art in vivo studies also revealed that inhibition of **IL-12** production has therapeutic effects against inflammatory disorders such as collagen induced arthritis, established colitis, experimental autoimmune encephalomyelitis, experimental autoimmune uveoretinitis and cyclophosphamide induced diabetes. (I) may be used in conjunction with other therapeutic agents, e.g. antiinflammatory agents.

In an animal study using Balb/c mice in which septic shock had been induced by single intradermal injection of LPS (1 mu g/ml) in the foot pad, 3 tested compounds (I) (unspecified) administered at 10-20 mg/kg/day for 3 days produced a survival rate of 60% and 80% in 2/5 groups, whilst all mice died in the groups that received no treatment or vehicle only.

ADVANTAGE - (I) are small non-protein compounds (cf. anti-**IL-12 antibodies** which can be unstable after administration and whose use in long term treatments of chronic diseases is expensive). Also, in a cytotoxicity assay, 4 out of 9 tested compounds (I) showed a lower cytotoxicity toward PBMC cell line compared to dexamethazone, and 3 (out of the same 9 compounds (I)) showed a lower cytotoxicity toward THP-1 cell line compared to dexamethazone.

Dwg.0/0

L13 ANSWER 11 OF 32 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
AN 2000-638250 [61] WPIDS
DNN N2000-473413 DNC C2000-191967
TI New human **antibody** specific for human interleukin-12 (**IL-12**) used to treat disorders characterized by aberrant **IL-12** expression e.g. Crohn's disease and **multiple sclerosis**.
DC B04 D16 S03 S05
IN BANERJEE, S; CARMEN, S; DERBYSHIRE, E J; DU FOU, S L; DUNCAN, A R; ELVIN, J G; FRIEDRICH, S; HOLTET, T L; KAYMAKCALAN, Z; LABKOVSKY, B; MYLES, A; PASKIND, M; ROGUSKA, M; SAKORAFAS, P; SALFELD, J G; SMITH, S; TRACEY, D E; VELDMAN, G M; VENTURINI, A; WARNE, N W; WHITE, M; WIDOM, A
PA (BADI) BASF AG; (GEMY) GENETICS INST INC
CYC 92
PI WO 2000056772 A1 20000928 (200061)* EN 395p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW

W: AE AG AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ
EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK
LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI
SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW

AU 2000039216 A 20001009 (200103)

ADT WO 2000056772 A1 WO 2000-US7946 20000324; AU 2000039216 A AU 2000-39216 20000324

FDT AU 2000039216 A Based on WO 200056772

PRAI US 1999-126603 19990325

AB WO 200056772 A UPAB: 20001128

NOVELTY - An isolated human **antibody** (I) or an antigen-binding portion that binds to human interleukin-12 (**IL-12**), and which is a neutralizing **antibody**, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a selectively mutated human interleukin-12 (**IL-12**) **antibody** (II) comprising a human **antibody** or an antigen-binding portion selectively mutated at a preferred selective mutagenesis, contact or hypermutation position with an activity enhancing amino acid residue such that it binds to human **IL-12**;

(2) an isolated human **antibody** (III) or an antigen-binding portion that binds to human **IL-12** and dissociates from human **IL-12** with a koff rate constant of 0.1s-1 or less, as determined by plasmon resonance, or which inhibits phytohemagglutinin blast proliferation in an in vitro phytohemagglutinin blast proliferation assay (PHA) with an IC50 of 1 x 10-6 or less;

(3) an isolated human **antibody** (IV) or an antigen-binding portion comprising the following characteristics:

(a) inhibits phytohemagglutinin blast proliferation in an in vitro PHA with an IC50 of 1 x 10-6 or less;

(b) a heavy chain CDR3 comprising 1 of 80 fully defined 6 amino acid sequences or a single 115 amino acid sequence (given in the specification); and

(c) a light chain CDR3 comprising 1 of 79 fully defined 12 amino acid sequences or a single 10 or 112 amino acid sequence (given in the specification);

(4) an isolated nucleic acid (V) encoding the heavy chain CDR3 having one of two fully defined 6 amino acid sequences (given in the specification);

(5) an isolated nucleic acid (VI) encoding the light chain CDR3 having one of two fully defined 12 amino acid sequences (given in the specification);

(6) an isolated human **antibody** (VII) or an antigen-binding portion as in (3) but where the heavy chain variable region comprises an amino acid sequence from a member of the VH3 germline family or the COS-3 germline, and a light chain variable region comprising an amino acid sequence from a member of the V lambda 1 germline family or the DPL8 germline, where the region has a mutation at a contact or hypermutation position with an activity enhancing amino acid residue;

(7) an isolated human **antibody** (VIII) or an antigen-binding portion as in (6) but where the heavy chain variable region comprises a CDR2 and CDR1 structurally similar to CDR2s and CDR1s from other VH3 germline family and a light chain variable region comprising a CDR2 and CDR1 structurally similar to CDR2s and CDR1s from other V lambda 1 germline family and which have a mutation at a contact or hypermutation position with an activity enhancing amino acid residue;

(8) a recombinant expression vector (IX) encoding:

(a) an **antibody** heavy chain having a variable region comprising a fully defined 115 amino acid sequence (given in the specification); and

(b) an **antibody** light chain having a variable region comprising a fully defined 112 amino acid sequence (given in the

specification)

(9) a host cell (X) into which (IX) has been introduced;

(10) a method of synthesizing a human **antibody** that binds human **IL-12** comprising culturing (X);

(11) an isolated human **antibody** (XI) or an antigen-binding portion that neutralizes the activity of human **IL-12** and at least one additional primate **IL-12** from baboon, marmoset, chimpanzee, cynomolgus or rhesus **IL-12** but not the activity of mouse **IL-12**;

(12) a pharmaceutical composition comprising (I-IV) and (VII-XI);

(13) a method for inhibiting human **IL-12** activity comprising contacting human **IL-12** with (IX);

(14) a method for inhibiting human **IL-12** activity in a human subject suffering from a disorder in which **IL-12** activity is detrimental comprising administering (IX);

(15) a method for improving the activity of an **antibody** or an antigen-binding portion to attain a predetermined target activity, comprising:

(a) providing a parent **antibody** or antigen-binding portion;

(b) selecting a preferred selective mutagenesis position from H30, H31, H31B, H33, H52, H56, H58, L30, L31, L32, L50, L91, L92, L93, L94 or L96;

(c) individually mutating the selected preferred selective mutagenesis position of at least two other amino acid residues to create a first panel of mutated **antibodies**;

(d) evaluating the activity of the first panel of mutated **antibodies** to determine if the mutation of (c) has produced an **antibody** with the predetermined target activity or partial target activity;

(e) combining in a stepwise fashion, in the parent **antibody**, individual mutations shown to have an improved activity, to form combination **antibodies**;

(f) evaluating the activity of the combination **antibodies**;

(g) if steps (d) or (f) do not result in an **antibody** having a predetermined target activity the method further comprises mutating additional amino acid residues from H35, H50, H53, H54, H95, H96, H97, H98, L30A or L96 to at least two other amino acid residues creating a second panel of mutated **antibodies**;

(h) evaluating the activity of the second panel of antibodies to determine if they possess the predetermined target activity;

(i) combining in a stepwise fashion, in the parent antibody, individual mutations in step (g) shown to have an improved activity, to form combination antibodies;

(j) evaluating the activity of the combination antibodies;

(k) if steps (h) or (j) do not result in an antibody having a predetermined target activity the method further comprises mutating additional amino acid residues from H33B, H52B or L31A to at least two other amino acid residues creating a third panel of mutated antibodies;

(l) evaluating the activity of the third panel of antibodies to determine if they possess the predetermined target activity;

(m) combining in a stepwise fashion, in the parent antibody, individual mutations in step (k) shown to have an improved activity, to form combination antibodies;

(n) evaluating the activity of the combination antibodies;

(16) a method for improving the activity of an antibody or an antigen-binding portion to attain a predetermined target activity as in (14) but where the preferred selective mutagenesis position, contact or hypermutation position is within a complementarity determining region; and

(17) a method for detecting human IL-12 comprising contacting human IL-12 with (I-IV) and (VII-XI).

ACTIVITY - Antirheumatic; antiarthritic; antisclerotic; antiinflammatory; neuroprotective; antipsoriatic; antiasthmatic; cardiant;

antiparasitic; antibacterial, immunosuppressive.
MECHANISM OF ACTION - Anti human IL-12 antibody.
USE - The antibodies or antigen-binding fragments are useful in the treatment of disorders associated with detrimental release of human IL-12,
especially Crohn's disease, multiple sclerosis and rheumatoid arthritis (claimed). They can also be used in the manufacture of a pharmaceutical composition to treat human IL-12 disorders (claimed). The nucleic acid, expression vector and recombinant cells can be used to produce an antibody
that specifically binds to human IL-12.
Dwg.0/14

L13 ANSWER 12 OF 32 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
AN 2000153043 EMBASE
TI Anti-interleukin-12 **antibody**: Potential role in preventing relapses of **multiple sclerosis**.
AU Fox R.J.; Rostami A.M.
CS Dr. A.M. Rostami, Department of Neurology, Univ. of Pennsylvania Medical Center, 3400 Spruce Street, Philadelphia, PA 19104-4283, United States. rostamia@mail.med.upenn.edu
SO BioDrugs, (2000) 13/4 (233-241).
Refs: 71
ISSN: 1173-8804 CODEN: BIDRF4
CY New Zealand
DT Journal; Article
FS 008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy
LA English
SL English
AB **Multiple sclerosis** is an inflammatory demyelinating disorder of the central nervous system. Immunological evidence from patients with **multiple sclerosis** and experimental models suggests that the cytokine interleukin-12 (**IL-12**) plays an important role in the pathogenesis of inflammatory demyelination. In experimental autoimmune encephalomyelitis, an animal model of **multiple sclerosis**, **antibodies** that block **IL-12** can prevent relapses of the disease. Anti-**IL-12 antibodies** present a novel approach for preventing relapses in **multiple sclerosis**.

L13 ANSWER 13 OF 32 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
AN 2000274868 EMBASE
TI Defective regulation of IFN.gamma. and **IL-12** by endogenous IL-10 in progressive MS.
AU Balashov K.E.; Comabella M.; Ohashi T.; Khoury S.J.; Weiner H.L.
CS Dr. H.L. Weiner, Center for Neurologic Diseases, Brigham and Women's Hospital, HIM-730, 77 Avenue Louis Pasteur, Boston, MA 02115-5817, United States. weiner@cnd.bwh.harvard.edu
SO Neurology, (2000) 55/2 (192-198).
Refs: 34
ISSN: 0028-3878 CODEN: NEURAI
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LA English
SL English
AB Background: MS is a chronic inflammatory disease of the CNS postulated to be a Th1 type cell-mediated autoimmune disease. There is increased interferon-.gamma. (IFN.gamma.) secretion in MS, and IFN.gamma. administration induces exacerbations of disease. IFN.gamma. expression is

closely regulated by a number of cytokines produced by different cells of the immune system. Interleukin-12 (**IL-12**) is a major factor leading to Th1-type responses, including IFN.gamma. secretion, and there is increased secretion of **IL-12** in MS. IL-10 is a potent inhibitor of both **IL-12** and IFN.gamma. expression. Methods: The authors investigated cytokine production and proliferative responses of peripheral blood mononuclear cells stimulated with soluble anti-CD3 in healthy controls and patients with stable relapsing-remitting MS or progressive MS. Results: The authors found that T cell receptor-mediated IFN.gamma. and IL-10 secretion were increased in progressive MS, whereas IL-4 and IL-2 secretion and lymphocyte proliferative responses were normal. Anti-**IL-12** **antibody** suppressed raised IFN.gamma. in progressive MS but did not affect raised IL-10. In addition, neutralization of endogenous IL-10 upregulated IFN.gamma. in controls but not progressive MS. IL-10 was produced by CD4+ cells whereas IFN.gamma. was produced by both CD4+ and CD8+ cells. There were no differences in IL-10 receptor expression in MS patients. Conclusions: These abnormalities in IL-10 regulation were not seen in the relapsing-remitting form of MS. Thus, the defect in regulation of both **IL-12** and IFN.gamma. production by endogenous IL-10 in progressive MS could be an important factor involved in the transition of MS from the relapsing to the progressive stage and has implications for treating MS patients with exogenous IL-10.

L13 ANSWER 14 OF 32 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
AN 1999432440 EMBASE
TI Anti-**IL-12** **antibody** prevents the development and progression of **multiple sclerosis**-like relapsing-remitting demyelinating disease in NOD mice induced with myelin oligodendrocyte glycoprotein peptide.
AU Ichikawa M.; Koh C.-S.; Inoue A.; Tsuyusaki J.; Yamazaki M.; Inaba Y.; Sekiguchi Y.; Itoh M.; Yagita H.; Komiyama A.
CS C.-S. Koh, Department of Medicine (Neurology), Shinshu University School Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. kshosei@hsp.md.shinshu-u.ac.jp
SO Journal of Neuroimmunology, (2000) 102/1 (56-66).
Refs: 43
ISSN: 0165-5728 CODEN: JNRIDW
PUI S 0165-5728(99)00153-8
CY Netherlands
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
LA English
SL English
AB Treatment with monoclonal anti-**IL-12** **antibody** injected on day 0, 7 and 10 after immunization with myelin oligodendrocyte glycoprotein (MOG) peptide 35-55 in NOD mice resulted in significant suppression of the development and the severity of the chronic relapsing-remitting experimental autoimmune encephalomyelitis (EAE) both clinically and histologically. The spleen cells from anti-**IL-12** **antibody** treated mice displayed markedly inhibited MOG35-55 specific proliferation and IFN-.gamma. production. MOG35-55 specific **antibody** production was enhanced by anti-**IL-12** **antibody** treatment. These results suggest that **IL-12** is critically involved in the pathogenesis of MOG-induced EAE and that **antibody** to **IL-12** could be an effective therapeutic agent in the clinical treatment of autoimmune demyelinating diseases such as **multiple** **sclerosis** (MS). Copyright (C) 2000 Elsevier Science B.V.

L13 ANSWER 15 OF 32 WPIDS COPYRIGHT 2001 DERWENT INFORMATION LTD
DUPLICATE
4
AN 1999-458684 [38] WPIDS
DNC C1999-134705
TI New **antibodies** to human interleukin-12, used for treating diseases associated with increased **IL-12** bioactivity such as autoimmune disorders, e.g. **multiple sclerosis**.
DC B04 D16
IN GATELY, M K; PRESKY, D H
PA (HOFF) HOFFMANN LA ROCHE & CO AG F; (HOFF) HOFFMANN LA ROCHE INC
CYC 85
PI WO 9937682 A2 19990729 (199938)* EN 46p
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SZ UG ZW
W: AL AM AT AU AZ BA BB BG BR BY CA CH CN CU CZ DE DK EE ES FI GB GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT UA UG UZ VN YU ZW
ZA 9900452 A 19990929 (199947) 48p
AU 9925177 A 19990809 (200001)
BR 9907743 A 20001017 (200056)
EP 1049717 A2 20001108 (200062) EN
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU NL PT SE
US 6225117 B1 20010501 (200126)
CN 1288468 A 20010321 (200137)
ADT WO 9937682 A2 WO 1999-EP202 19990115; ZA 9900452 A ZA 1999-452 19990121; AU 9925177 A AU 1999-25177 19990115; BR 9907743 A BR 1999-7743 19990115, WO 1999-EP202 19990115; EP 1049717 A2 EP 1999-904780 19990115, WO 1999-EP202 19990115; US 6225117 B1 Provisional US 1998-72333 19980123, US 1999-232522 19990119; CN 1288468 A CN 1999-802310 19990115
FDT AU 9925177 A Based on WO 9937682; BR 9907743 A Based on WO 9937682; EP 1049717 A2 Based on WO 9937682
PRAI US 1998-72333 19980123; US 1999-232522 19990119
AB WO 9937682 A UPAB: 19991122
NOVELTY - New **antibodies** to human interleukin-12 are produced using a mammal which is deficient in the gene encoding the p35 or p40 subunit of **IL-12**.
DETAILED DESCRIPTION - (A) An **antibody** to the human interleukin (**IL**)-**12** p75 heterodimer which consists of a p35 subunit and a p40 subunit, where the **antibody**:
(i) immunologically reacts with an epitope presented by the p75 heterodimer of human **IL-12**, but is not immunologically reactive with an epitope presented by the p40 subunit; and
(ii) is produced from a mammal, preferably a mouse which is deficient in the gene encoding the p35 subunit or the p40 subunit of **IL-12**.
INDEPENDENT CLAIMS are also included for the following:
(1) a monoclonal **antibody** (MAb) to human **IL-12** which consists of a p35 subunit and a p40 subunit forming a p75 heterodimer, where the MAb;
(i) immunologically reacts with an epitope presented by the p75 heterodimer of human **IL-12**, but is not immunologically reactive with any epitope presented by the p40 subunit; and
(ii) neutralizes at least 90% of the bioactivity of human **IL-12**;
(2) a hybridoma that produces an **antibody** as in (A) or (1).
ACTIVITY - The **antibodies** can neutralize **IL-12** bioactivity as determined by ability to block **IL-12** stimulated phytohemagglutinin A (PHA)-activated lymphoblast proliferation and interferon- gamma production by PHA-activated lymphoblasts. The 5F2, 16F2, 16G2 and 20E11 **antibodies** were able to inhibit human **IL-12** stimulated PHA activated human lymphoblast proliferation by at least 90%. These anti-human heterodimer

specific **IL-12 antibodies** were able to inhibit greater than 90% of **IL-12** stimulated IFN-gamma production when used at 0.5 micro g/ml.

USE - The **antibodies** can be used for controlling diseases with pathologies that are mediated through immune mechanisms, particularly diseases associated with increased **IL-12** bioactivity that results in aberrant Th1-type helper cell activity like autoimmune disorders, e.g. **multiple sclerosis**, rheumatoid arthritis, autoimmune diabetes mellitus, and inflammatory bowel disease (IBD) including Crohn's disease and ulcerative colitis (claimed). They can also be used to treat transplantation/graft-versus-host disease and septic shock.

ADVANTAGE - The anti-**IL-12 antibodies** exhibit higher potency and greater efficacy than known heterodimer specific **IL-12 antibodies**.

Dwg.0/7

L13 ANSWER 16 OF 32 USPATFULL
AN 1999:163661 USPATFULL
TI Interferon stimulating protein and uses thereof
IN Hilbert, David M., Bethesda, MD, United States
Bednarik, Daniel P., Columbia, MD, United States
Nardelli, Bernadetta, Gaithersburg, MD, United States
Murphy, Marianne, Richmond, United Kingdom
Parmelee, David, Rockville, MD, United States
Gronowski, Ann, Ballwin, MO, United States
Schreiber, Robert, St. Louis, MO, United States
PA Humn Genome Sciences, Inc., Rockville, MD, United States (U.S. corporation)
Washington University, St. Louis, MO, United States (U.S. corporation)
PI US 6001806 19991214
AI US 1998-105039 19980626 (9)
PRAI US 1997-51053 19970627 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: MacMillan, Keith D.; Assistant Examiner: Wessendorf, T. D.
LREP Hoover, Kenley K.
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 13 Drawing Figure(s); 15 Drawing Page(s)
LN.CNT 3165
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to the use of the baculovirus glycoprotein, Interferon Stimulating Protein (ISP) (also known as gp67, gp64 EFP, or gp64), or the gene sequence encoding ISP, to stimulate production of interferon, such as for immunotherapy, anti-viral, anti-cancer, anti-bacterial, or anti-parasitic therapy. This invention also relates to novel mutant forms of ISP that show enhanced biological (i.e., anti-viral) activity, increased stability, higher yield or better solubility.

L13 ANSWER 17 OF 32 USPATFULL
AN 1999:146562 USPATFULL
TI Compositions and methods for decreasing IGIF and IFN-.gamma. production by administering an ICE inhibitor
IN Su, Michael, Newton, MA, United States
Gu, Yong, Brookline, MA, United States
Livingston, David J., Newtonville, MA, United States
PA Vertex Pharmaceuticals, Inc., Cambridge, MA, United States (U.S. corporation)
PI US 5985863 19991116

AI US 1996-712878 19960912 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Jordan, Kimberly
LREP Fish & Neave, Haley, Jr., James F., Dixon, Lisa A.
CLMN Number of Claims: 17
ECL Exemplary Claim: 1
DRWN 6 Drawing Figure(s); 35 Drawing Page(s)
LN.CNT 1766
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to methods and pharmaceutical compositions
for decreasing the production of interferon-gamma inducing factor (IGIF). The invention also relates to methods and pharmaceutical compositions for decreasing the production of interferon-gamma (IFN-.gamma.). The compositions comprise a therapeutically effective amount of a compound which inhibits interleukin-1.beta. converting enzyme (ICE) and a pharmaceutically acceptable carrier. The methods comprise the step of administering the above compositions to a subject. The present invention also relates to methods for treating or reducing the advancement, severity or effects of an IGIF- or IFN-.gamma.-mediated
inflammatory, infectious or autoimmune condition.

L13 ANSWER 18 OF 32 USPATFULL
AN 1999:110204 USPATFULL
TI Human growth-related CDC10 homolog
IN Hillman, Jennifer L., Mountain View, CA, United States
Yue, Henry, Sunnyvale, CA, United States
Guegler, Karl J., Menlo Park, CA, United States
Kaser, Matthew R., Castro Valley, CA, United States
Mathur, Preete, Fremont, CA, United States
PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)
PI US 5952214 19990914
AI US 1998-205681 19981204 (9)
RLI Division of Ser. No. US 1997-978182, filed on 25 Nov 1997, now patented,
Pat. No. US 5849556
DT Utility
FS Granted
EXNAM Primary Examiner: Wax, Robert A.; Assistant Examiner: Mayhew, Bradley S.
LREP Incyte Pharmaceuticals, Inc, Mohan-Peterson, Sheela
CLMN Number of Claims: 2
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 2445
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a human growth-related CDC10 homolog (GR-SEP) and
polynucleotides which identify and encode GR-SEP. The invention also provides expression vectors, host cells, agonists, **antibodies** and antagonists. The invention also provides methods for treating and preventing disorders associated with expression of GR-SEP.

L13 ANSWER 19 OF 32 USPATFULL
AN 1999:89052 USPATFULL
TI Human nucleolin-like protein
IN Bandman, Olga, Mountain View, CA, United States
Yue, Henry, Sunnyvale, CA, United States
Corley, Neil C., Mountain View, CA, United States
Shah, Purvi, Sunnyvale, CA, United States
PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

PI US 5932475 19990803
AI US 1997-990114 19971212 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Huff, Sheela
LREP Incyte Pharmaceuticals, Inc.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 2215
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a human nucleolin-like protein (HNLP) and polynucleotides which identify and encode HNLP. The invention also provides expression vectors, host cells, **antibodies**, agonists, and antagonists. The invention also provides methods for treating or preventing disorders associated with expression of HNLP.

L13 ANSWER 20 OF 32 CAPLUS COPYRIGHT 2001 ACS
AN 1999:551169 CAPLUS
DN 131:285263
TI Role of endogenous interleukin-12 (**IL-12**) in induced and spontaneous relapses of experimental autoimmune encephalomyelitis in mice
AU Heremans, Hubertine; Dillen, Chris; Groenen, Marleen; Matthys, Patrick; Billiau, Alfons
CS Laboratory of Immunobiology, Rega Institute, University of Leuven Medical School, Louvain, B-3000, Belg.
SO Eur. Cytokine Network (1999), 10(2), 171-179
CODEN: ECYNEJ; ISSN: 1148-5493
PB John Libbey Eurotext
DT Journal
LA English
AB Actively induced, chronic relapsing exptl. autoimmune encephalomyelitis (CREAE) was studied in SJL/J and in Biozzi ABH mice. In Biozzi ABH mice, relapses occurred spontaneously with high frequency. In SJL/J mice, spontaneous relapses occurred infrequently; however they could be induced reproducibly by reimmunization. In both models, moderately increased levels of serum **IL-12**(p40) were consistently found shortly before primary attacks, but irregularly at later times. Injections of anti-**IL-12 antibody** inhibited disease development in both SJL/J and in Biozzi ABH mice. The time window during which treatment needed to be initiated to be effective, ranged from before induction until shortly before the symptoms of primary attacks emerged. Such treatment inhibited not only the first attack but also the spontaneous or induced relapses. Most significantly, anti-**IL-12 antibody** given during remission of primary disease inhibited actively re-induced relapses in SJL/J, but not spontaneous relapses in Biozzi ABH mice. Thus, endogenous **IL-12** favors EAE development by crucially affecting the active induction process, but a second burst of **IL-12** prodn. may not be necessary for triggering spontaneous relapses.
RE.CNT 41
RE
(2) Billiau, A; J Immunol 1988, V140, P1506 CAPLUS
(3) Bright, J; J Neuroimmunol 1998, V82, P22 CAPLUS
(5) Cannella, B; J Neurosci Res 1996, V45, P735 CAPLUS
(6) Constantinescu, C; J Immunol 1998, V161, P5097 CAPLUS
(7) Duong, T; J Neuroimmunol 1992, V36, P105 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 21 OF 32 BIOSIS COPYRIGHT 2001 BIOSIS
AN 2000:83810 BIOSIS
DN PREV200000083810

TI **IL-12** reverses the suppressive effect of the CD40 ligand blockade on experimental autoimmune encephalomyelitis (EAE.
AU Constantinescu, Cris S.; Hilliard, Brendan; Wysocka, Maria; Ventura, Elvira S.; Bhopale, Mahendra K.; Trinchieri, Giorgio; Rostami, A. M. (1)
CS (1) Department of Neurology, University of Pennsylvania, Philadelphia, PA, 19104 USA
SO Journal of the Neurological Sciences, (Dec. 1, 1999) Vol. 171, No. 1, pp. 60-64.
ISSN: 0022-510X.
DT Article
LA English
SL English
AB Blockade of the CD40 ligand (CD40L)-CD40 interaction suppresses experimental autoimmune encephalomyelitis (EAE). Since this interaction induces **IL-12**, an essential cytokine for EAE induction, we hypothesized that CD40L blockade may suppress EAE through **IL-12** inhibition. Here we show that exogenous **IL-12** abolishes the ability of anti-CD40L monoclonal **antibodies** to prevent EAE. Anti-**IL-12** **antibodies** prevent this reversal and protect from EAE. These results show that **IL-12** is sufficient to overcome CD40L blockade and suggest that, of the multiple consequences of the CD40L-CD40 interaction, **IL-12** induction is an essential one for induction of EAE.

L13 ANSWER 22 OF 32 USPATFULL
AN 1998:161997 USPATFULL
TI **Antibody** to interleukin-12 receptor
IN Gately, Maurice Kent, Pine Brook, NJ, United States
Presky, David Howard, Glen Ridge, NJ, United States
Wu, Chang-you, Belleville, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5853721 19981229
AI US 1995-381059 19950131 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Sun-Hoffman, Lin
LREP Johnston, George W., Tramaloni, Dennis P., Kass, Alan P.
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN 33 Drawing Figure(s); 22 Drawing Page(s)
LN.CNT 1418
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a novel **antibody** against the **IL-12** receptor and a novel combination of anibodies anainst the **IL-12** receptor. The novel anti-**IL-12** receptor anbody, designated as 2B10, provided in accordance with the present invention binds to the human **IL-12** receptor but which is not capable of inhibiting the binding of human **IL-12** to the high affinity human **IL-12** receptor and is not capable of neutralizing human **IL-12** bioactivity by binding to human **IL-12** receptor.

L13 ANSWER 23 OF 32 USPATFULL
AN 1998:157165 USPATFULL
TI Human growth-related CDC10 homolog
IN Hillman, Jennifer L., Mountain View, CA, United States
Yue, Henry, Sunnyvale, CA, United States
Guegler, Karl J., Menlo Park, CA, United States
Kaser, Matthew R., Castro Valley, CA, United States
Mathur, Preete, Fremont, CA, United States
PA Incyte Pharmaceuticals, Inc., Palo Alto, CA, United States (U.S. corporation)

PI US 5849556 19981215
AI US 1997-978182 19971125 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Hendricks, Keith D.; Assistant Examiner: Mayhew, Bradley S.
LREP Incyte Pharmceuticals, Inc.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 9 Drawing Figure(s); 9 Drawing Page(s)
LN.CNT 2398
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention provides a human growth-related CDC10 homolog (GR-SEP) and polynucleotides which identify and encode GR-SEP. The invention also provides expression vectors, host cells, agonists, **antibodies** and antagonists. The invention also provides methods for treating and preventing disorders associated with expression of GR-SEP.

L13 ANSWER 24 OF 32 USPATFULL
AN 1998:135151 USPATFULL
TI Human receptor for interleukin-12
IN Chua, Anne On, Wayne, NJ, United States
Gubler, Ulrich Andreas, Glen Ridge, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5831007 19981103
AI US 1995-419652 19950411 (8)
RLI Division of Ser. No. US 1994-248532, filed on 31 May 1994, now patented, Pat. No. US 5536657 which is a continuation-in-part of Ser. No. US 1993-94713, filed on 19 Jul 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Ulm, John
LREP Johnston, George W., Epstein, William H., Bucholz, Briana C.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 35 Drawing Figure(s); 26 Drawing Page(s)
LN.CNT 1937
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to substantially pure Interleukin-12 receptor cDNAs and protein and uses therefore. The Interleukin-12 receptor is shown to be a member of the cytokine receptor superfamily and has a high homology to human gp130.

L13 ANSWER 25 OF 32 CAPLUS COPYRIGHT 2001 ACS
AN 1998:251074 CAPLUS
DN 128:307519
TI Methods for enhancing oral tolerance and treating autoimmune disease using inhibitors of interleukin-12
IN Strober, Warren; Kelsall, Brian L.; Marth, Thomas
PA United States Dept. of Health and Human Services, USA; Strober, Warren; Kelsall, Brian L.; Marth, Thomas
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9816248	A1	19980423	WO 1996-US16007	19961011
	W: AU, CA, JP, US				
	AU 9672576	A1	19980511	AU 1996-72576	19961011

PRAI WO 1996-US16007 19961011
AB The present invention provides a method for enhancing oral tolerance to an antigen assocd. with an autoimmune disease in a subject having the autoimmune disease comprising orally administering to the subject an antigen assocd. with the autoimmune disease and administering an inhibitor of interleukin-12 in amts. sufficient to enhance oral tolerance. Also provided in the present invention is a method for treating or preventing an autoimmune disease in a subject comprising orally administering to the subject an antigen assocd. with the autoimmune disease and administering an inhibitor of interleukin-12 in amts. sufficient to treat or prevent the autoimmune disease, thereby treating or preventing the autoimmune disease.
The interleukin 12 inhibitor is an **antibody** or monoclonal **antibody**.

L13 ANSWER 26 OF 32 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5
AN 1998385328 EMBASE
TI Suppressive effect on Theiler's murine encephalomyelitis virus-induced demyelinating disease by the administration of anti-**IL-12 antibody**.
AU Inoue A.; Koh C.-S.; Yamazaki M.; Yahikozawa H.; Ichikawa M.; Yagita H.; Kim B.S.
CS Dr. C.-S. Koh, Third Dept. of Medicine (Neurology), Shinshu Univ. School of Medicine, 3-1-1 Asahi, Matsumoto 390-8621, Japan. kshosel@hsp.md.shinshu-u.ac.jp
SO Journal of Immunology, (15 Nov 1998) 161/10 (5586-5593).
Refs: 46
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
LA English
SL English
AB We examined the role of **IL-12**, a cytokine critical to the evolution of cellular responses, in the development of Theiler's murine encephalomyelitis virus-induced demyelinating disease (TMEV-IDD). Treatment with mAbs to **IL- 12**, especially during the effector phase, resulted in significant suppression of the development of this disease both clinically and histologically. In mice treated with these mAbs, the production of inflammatory and Th1-derived cytokines such as TNF-.alpha. and lieN-.gamma., in the spleen cells was decreased, and that of Th2-derived cytokines such as IL-4 and IL-10 was increased. The delayed type hypersensitivity and T cell proliferative response specific for TMEV were decreased by this treatment. These data suggest that **IL-12** is critically involved in the pathogenesis of TMEV-IDD and that Abs to **IL-12** could be a novel therapeutic approach in the clinical treatment of demyelinating diseases such as human **multiple sclerosis**.

L13 ANSWER 27 OF 32 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 6
AN 1998134307 EMBASE
TI The interleukin-12/interleukin-12-receptor system: Role in normal and pathologic immune responses.
AU Gately M.K.; Renzetti L.M.; Magram J.; Stern A.S.; Adorini L.; Gubler U.; Presky D.H.
CS M.K. Gately, Via Olgettina 58, 20132 Milano, Italy. maurice.gately@roche.com
SO Annual Review of Immunology, (1998) 16/- (495-521).

Refs: 169
ISSN: 0732-0582 CODEN: ARIMDU
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
LA English
SL English
AB Interleukin-12 (**IL-12**) is a heterodimeric cytokine that plays a central role in promoting type 1 T helper cell (Th1) responses and, hence, cell- mediated immunity. Its activities are mediated through a high-affinity receptor composed of two subunits, designated .beta.1 and .beta.2. Of these two subunits, .beta.2 is more restricted in its distribution, and regulation of its expression is likely a central mechanism by which **IL-12** responsiveness is controlled. Studies with neutralizing anti-**IL-12** **antibodies** and **IL-12**- deficient mice have suggested that endogenous **IL-12** plays an important role in the normal host defense against infection by a variety of intracellular pathogens. However, **IL-12** appears also to play a central role in the genesis of some forms of immunopathology. Inhibition of **IL-12** synthesis or activity may be beneficial in diseases associated with pathologic Th1 responses, such as **multiple sclerosis** or Crohn's disease. On the other hand, administration of recombinant **IL-12** may have utility in the treatment of diseases associated with pathologic Th2 responses such as allergic disorders and asthma.

L13 ANSWER 28 OF 32 CAPLUS COPYRIGHT 2001 ACS
AN 1998:121509 CAPLUS
DN 128:256270
TI Expression of **IL-12** in CNS and lymphoid organs of mice with experimental allergic encephalitis
AU Bright, John J.; Musuro, Bola F.; Du, Caigan; Sriram, Subramaniam
CS 2201 Capers Avenue, 1222 Vanderbilt Stallworth Rehabilitation Hospital, Multiple Sclerosis Research Laboratory, Nashville, TN, 37212, USA
SO J. Neuroimmunol. (1998), 82(1), 22-30
CODEN: JNRIDW; ISSN: 0165-5728
PB Elsevier Science B.V.
DT Journal
LA English
AB EAE is a Th1 cell-mediated inflammatory autoimmune demyelinating disease of the central nervous system. **IL-12** is a 70 kDa heterodimeric cytokine, capable of regulating a wide range of immune functions. In view of its crucial role in the development of Th1 immune responses, we studied the expression of **IL-12** p40 in the CNS and lymphoid organs of mice with EAE. RT-PCR anal. showed an increase in the expression of **IL-12** p40 in brain and spinal cord during the acute paralytic phase of EAE and that decreased upon clin. recovery. The expression of p40 mRNA was also increased in spleen, lymph node and liver along with an elevated levels of circulating serum **IL-12** during the height of disease. In vivo administration of rIL-12 increased the proliferative response and IFN-.gamma. prodn. of MBP sensitized T cells and that was decreased following treatment with anti-**IL-12** **antibody** . The expression of **IL-12** in the target and lymphoid organs of animals with EAE, the induction of a Th1 type immune response following immunization with neuronal antigens and the inhibition of clin. disease upon treatment with anti-**IL-12** **antibody** suggest the crucial role of **IL-12** in the pathogenesis of EAE.

L13 ANSWER 29 OF 32 USPATFULL
AN 97:80900 USPATFULL

TI **IL-12** inhibition of B1 cell activity
IN Metzger, Dennis W., Sylvania, OH, United States
Van Cleave, Victor H., Londonderry, NH, United States
PA Genetics Institute, Cambridge, MA, United States (U.S. corporation)
Medical College of Ohio, Toledo, OH, United States (U.S. corporation)
PI US 5665347 19970909
AI US 1995-382658 19950202 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Achutamurthy, Ponnathapura
LREP Hamilton, Brook, Smith & Reynolds, P.C.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1,2
DRWN 47 Drawing Figure(s); 18 Drawing Page(s)
LN.CNT 942
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a method of suppressing B1 cell activity in a host (e.g., mammalian, including human) comprising administering to the host an effective amount of **IL-12** that significantly suppresses or inhibits B1 cell activity. In addition, the invention relates to a method of treating a B1 cell disorder in a host, comprising administering to the host an effective therapeutic amount of **IL-12**. The invention further encompasses a method of screening for substances (e.g., proteins, peptides, small molecules) which enhance or suppress the inhibition of B1 cell activity by **IL-12**. The invention also relates to a substance identified by the methods of screening for a substance which enhances or suppresses **IL-12** inhibition of B1 cell activity.

L13 ANSWER 30 OF 32 USPATFULL
AN 97:64091 USPATFULL
TI P-40 homodimer of interleukin-12
IN Gately, Maurice Kent, Pine Brook, NJ, United States
Hakimi, John, Scarsdale, NY, United States
Ling, Ping, Nutley, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5650492 19970722
AI US 1995-424682 19950418 (8)
RLI Continuation of Ser. No. US 1993-87832, filed on 2 Jul 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Ulm, John; Assistant Examiner: Mertz, Prema
LREP Johnston, George W., Tramaloni, Dennis P., Kass, Alan P.
CLMN Number of Claims: 8
ECL Exemplary Claim: 1
DRWN 18 Drawing Figure(s); 12 Drawing Page(s)
LN.CNT 854
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Analysis of the culture media of p40-transfected COS cells indicated the presence of 40 kDa monomers and 80 kDa disulfide-linked homodimers. Examination of partially purified p40 recombinant proteins demonstrated that only the homodimer but not the monomer binds to the **IL-12** receptor. Partially purified 80 kDa homodimer inhibited [.sup.125 I]**IL-12** binding to PHA-activated human lymphoblasts with an IC.sub.50 of 80 ng/ml, which is similar to the IC.sub.50 value (20 ng/ml) for the human **IL-12** heterodimer. Although neither the 40 kDa monomer nor the 80 kDa dimer could stimulate human PHA-blast proliferation, the 80 kDa dimer inhibited **IL-12**-induced proliferation in a dose-dependent manner with an IC.sub.50 of 1 .mu.g/ml. The **IL-12** p40 subunit contains the essential epitopes for receptor

binding, but they are only active when p40 is covalently associated with a second protein such as p35 or p40. When p40 is associated with the p35 subunit, the heterodimer acts as an agonist mediating biologic activity. When p40 associates with itself, the homodimer behaves as an **antagonist**.

L13 ANSWER 31 OF 32 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 7
AN 97036980 EMBASE
DN 1997036980
TI Increased interleukin 12 production in progressive **multiple sclerosis**: Induction by activated CD4+ T cells via CD40 ligand.
AU Balashov K.E.; Smith D.R.; Khoury S.J.; Hafler D.A.; Weiner H.L.
CS H.L. Weiner, Center for Neurologic Diseases, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115, United States. weiner@cnd.bwh.harvard.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (1997) 94/2 (599-603).
Refs: 33
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LA English
SL English
AB **Multiple sclerosis** (MS) is a chronic inflammatory disease of the central nervous system postulated to be a cell-mediated autoimmune disease in which interferon .gamma. (IFN-.gamma.) plays an important role. There is increased IFN-.gamma. secretion in MS, and IFN-.gamma. administration induces exacerbations of disease. We found that interleukin 12 (**IL-12**) was responsible for raised IFN-.gamma. secretion in MS as anti-**IL-12** **antibodies** reversed raised anti-CD3-induced IFN-.gamma. in MS patients to normal levels. Furthermore, we found a marked increase in T cell receptor-mediated **IL-12** secretion in progressive MS patients vs. controls (24.8 .+-. 7.7 pg/ml vs. 1.5 .+-. 1.0 pg/ml, P = 0.003) and vs. relapsing-remitting patients (3.7 .+-. 1.4 pg/ml, P < 0.05). Investigation of the cellular basis for raised **IL-12** demonstrated that T cells from MS patients induced **IL-12** secretion from non-T cells, and that T cells from MS patients could even drive non-T cells from normal subjects to produce increased **IL-12**. Anti-CD40 ligand **antibody** completely blocked **IL-12** secretion induced by activated T cells, and we found increased CD40 ligand expression by activated CD4+ T cells in MS patients vs. controls. The CD40 ligand-dependent Th1-type immune activation was observed in the progressive but not in the relapsing-remitting form of MS, suggesting a link to disease pathogenesis and progression and providing a basis for immune intervention in the disease.

L13 ANSWER 32 OF 32 USPATFULL
AN 96:63048 USPATFULL
TI Recombinant DNA encoding human receptor for interleukin-12
IN Chua, Anne O., Wayne, NJ, United States
Gubler, Ulrich A., Glen Ridge, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5536657 19960716
AI US 1994-248532 19940531 (8)

RLI Continuation-in-part of Ser. No. US 1993-94713, filed on 19 Jul 1993, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Ulm, John
LREP Gould, George M., Johnston, George W., Kass, Alan P.
CLMN Number of Claims: 10
ECL Exemplary Claim: 1
DRWN 34 Drawing Figure(s); 25 Drawing Page(s)
LN.CNT 1755
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention relates to substantially pure Interleukin-12 receptor cDNAs and protein and uses therefore. The Interleukin-12 receptor is shown to be a member of the cytokine receptor superfamily and has a high homology to human gp130.

=> d clm 1 8 22

L13 ANSWER 1 OF 32 USPATFULL
CLM What is claimed is:
1. A purified polypeptide comprising an amino acid sequence selected from the group consisting of: a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-9, b) a naturally-occurring amino acid sequence having at least 95% sequence identity to the sequence selected from the group consisting of SEQ ID NO:1-2, 4, 6-7 and 9, wherein said amino acid sequence encodes a polypeptide having protein kinase activity, c) a biologically-active fragment of the amino acid sequence selected from the group consisting of SEQ ID NO:1-2, 4, 6-7 and 9, wherein said biologically-active fragment encodes a polypeptide having protein kinase activity, and d) an immunogenic fragment of the amino acid sequence selected from the group consisting of SEQ ID NO:1-2, 4, 6-7 and 9, wherein said polypeptides is capable of generating **antibody** that specifically binds to the polypeptide selected from the group consisting of SEQ ID NO:1-2, 4, 6-7 and 9.

2. An isolated polypeptide of claim 1, having a sequence selected from the group consisting of SEQ ID NO:1-9.

3. A composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable carrier.

4. A composition of claim 3, wherein the polypeptide has the sequence selected from the group consisting of SEQ ID NO: 1-9.

L13 ANSWER 8 OF 32 USPATFULL
CLM What is claimed is:
1. A method for modulating responsiveness to a corticosteroid in a subject, comprising administering to the subject suffering from a condition normally responsive to corticosteroid therapy: an interleukin-1 .beta. converting enzyme (ICE) inhibitor being administered at a dosage and by a route sufficient to inhibit production of IFN-.gamma. in the subject; and a corticosteroid, such that responsiveness of the subject to the corticosteroid is modulated as compared to when a corticosteroid alone is administered to the subject.

2. The method of claim 1, wherein the ICE inhibitor is an IFN-.gamma. inducing factor (IGIF) **antagonist**, the ICE inhibitor being administered at a dosage and by a route sufficient to inhibit IGIF

activity in the subject.

3. The method of claim 1, wherein the corticosteroid is selected from the group consisting of cortisone, hydrocortisone, beclomethasone, flunisolide, prednisone, prednisolone, methylprednisolone, triamcinolone, deflazacort, betamethasone and dexamethasone.

4. The method of claim 1, wherein the subject is suffering from septic shock.

5. The method of claim 1, wherein the subject is suffering from Crohn's disease.

6. The method of claim 1, wherein the subject is suffering from asthma.

7. The method of claim 1, wherein the subject is suffering from graft versus host disease or transplant rejection.

8. The method of claim 1, wherein the subject is suffering from an autoimmune disease or disorder.

9. The method of claim 1, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of asthma, adult respiratory distress syndrome, systemic lupus erythematosus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, **multiple sclerosis**, insulin-dependent diabetes mellitus, autoimmune arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, inflammatory pulmonary syndrome, pemphigus vulgaris, idiopathic thrombocytopenic purpura, autoimmune meningitis, myasthenia gravis, autoimmune thyroiditis, dermatitis, atopic dermatitis, eczematous dermatitis, psoriasis, Sjogren's Syndrome, keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, Stevens-Johnson syndrome, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Graves ophthalmopathy, primary biliary cirrhosis, uveitis posterior and interstitial lung fibrosis.

10. The method of claim 1, wherein the subject is suffering from an acute inflammatory disorder.

11. The method of claim 1, wherein the subject is suffering from a chronic inflammatory disorder.

12. The method of claim 1, wherein the ICE inhibitor and corticosteroid are administered such that steroid resistance in the subject is reversed, as compared to when a corticosteroid alone is administered to the subject.

13. The method of claim 1, wherein the ICE inhibitor and corticosteroid are administered such that steroid sensitivity in the subject is increased, as compared to when a corticosteroid alone is administered to the subject.

14. The method of claim 1, wherein the ICE inhibitor and the corticosteroid are administered to the subject according to a schedule that reduces the dosage of the corticosteroid over time and e method ameliorates a steroid rebound effect associated with administration of reduced dosages of the corticosteroid.

15. A method for modulating responsiveness to corticosteroids in a subject, comprising administering to the subject suffering from a condition normally responsive to corticosteroid therapy, an interleukin-1 .beta. converting enzyme (ICE) inhibitor; and a corticosteroid, such that responsiveness of the subject to the corticosteroid is modulated as compared to when a corticosteroid alone is administered to the subject.

16. The method of claim 15, wherein the corticosteroid is selected from the group consisting of cortisone, hydrocortisone, beclomethasone, flunisolide, prednisone, prednisolone, methylprednisolone, triamcinolone, deflazacort, betamethasone and dexamethasone.

17. The method of claim 15, wherein the subject is suffering from septic shock.

18. The method of claim 15, wherein the subject is suffering from Crohn's disease.

19. The method of claim 15, wherein the subject is suffering from asthma.

20. The method of claim 15, wherein the subject is suffering from graft versus host disease or transplant rejection.

21. The method of claim 15, wherein the subject is suffering from an autoimmune disease or disorder.

22. The method of claim 15, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of asthma, adult respiratory distress syndrome, systemic lupus erythematosus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, **multiple sclerosis**, insulin-dependent diabetes mellitus, autoimmune arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, inflammatory pulmonary syndrome, pemphigus vulgaris, idiopathic thrombocytopenic purpura, autoimmune meningitis, myasthenia gravis, autoimmune thyroiditis, dermatitis, atopic dermatitis, eczematous dermatitis, psoriasis, Sjogren's Syndrome, keratoconjunctivitis sicca secondary to Sjogren's Syndrome, alopecia areata, allergic responses due to arthropod bite reactions, aphthous ulcer, iritis, conjunctivitis, keratoconjunctivitis, cutaneous lupus erythematosus, scleroderma, vaginitis, proctitis, drug eruptions, Stevens-Johnson syndrome, leprosy reversal reactions, erythema nodosum leprosum, autoimmune uveitis, allergic encephalomyelitis, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, polychondritis, Wegener's granulomatosis, chronic active hepatitis, Graves ophthalmopathy, primary biliary cirrhosis, uveitis posterior and interstitial lung fibrosis.

23. The method of claim 15, wherein the subject is suffering from an acute inflammatory disorder.

24. The method of claim 15, wherein the subject is suffering from a chronic inflammatory disorder.

25. The method of claim 24, wherein the ICE inhibitor and the corticosteroid are administered such that steroid resistance in the subject is reversed, as compared to when a corticosteroid alone is administered to the subject.

26. The method of claim 24, wherein the ICE inhibitor and the corticosteroid are administered such that steroid sensitivity in the

subject is increased, as compared to when a corticosteroid alone is administered to the subject.

27. The method of claim 24, wherein the ICE inhibitor and the corticosteroid are administered to the subject according to a schedule that reduces the dosage of the corticosteroid over time and the method ameliorates a steroid rebound effect associated with administration of reduced dosages of the corticosteroid.

28. A method for modulating responsiveness to a corticosteroid in a subject, comprising: selecting a subject in need of modulation of responsiveness to a corticosteroid, wherein the subject suffers from a condition normally responsive to corticosteroid therapy; and administering to the subject an interleukin-1 .beta. converting enzyme (ICE) inhibitor which antagonizes a factor that regulates production of interferon (IFN-.gamma.) in the subject, the ICE inhibitor being administered at a dosage and by a route sufficient to inhibit production of IFN-.gamma. in the subject, such that responsiveness of the subject to a corticosteroid is modulated as compared to when a corticosteroid alone is administered to the subject.

29. The method of claim 28, wherein the subject is resistant to a corticosteroid prior to administration of the ICE inhibitor.

30. The method of claim 28, wherein the subject is responsive to a corticosteroid prior to administration of the ICE inhibitor but exhibits increased sensitivity to the corticosteroid after administration of the ICE inhibitor.

31. The method of claim 28, wherein treatment of the subject with a corticosteroid is to be stopped and administration of the ICE inhibitor ameliorates a steroid rebound effect in the subject.

32. The method of claim 28, wherein the ICE inhibitor is an IFN-.gamma. inducing factor (IGIF) **antagonist**, the ICF inhibitor being administered at a dosage and by a route sufficient to inhibit IGIF activity in the subject.

33. A method for modulating responsiveness to corticosteroids in a subject comprising administering to the subject suffering from a condition normally responsive to corticosteroid therapy: an interleukin-1.beta. converting enzyme (ICE) inhibitor compound having the structure of Formula I: ##STR6## wherein R.sup.1 is hydrogen, C.sub.1 -C.sub.6 alkyl, or benzyl; R.sup.2 is --CHO, --COR.sup.a, or --CN; each R.sup.a is independently hydrogen or C.sub.1 -C.sub.6 alkyl; X is a bond, CH.sub.2, CHR.sup.5, NH, NR.sup.5, or O; R.sup.3 is aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, cycloalkyl, substituted-cycloalkyl, heterocycle, or substituted-heterocycle; Y is absent, NR.sup.5, CO, S, O, SO.sub.2, --O(CHR.sup.5).sub.n --, CHR.sup.5, NR.sup.5 CO, NC(O)R.sup.5, CONR.sup.5, OCHR.sup.5, CHR.sup.5 O, SCHR.sup.5, CHR.sup.5 S, SO.sub.2 NR.sup.5, C.sub.1 -C.sub.6 alkyl, NR.sup.5 SO.sub.2, CH.sub.2 CHR.sup.5, CHR.sup.5 CH.sub.2, COCH.sub.2, or CH.sub.2 CO; R.sup.4 is absent, aryl, substituted-aryl, C.sub.1 -C.sub.8 alkyl, heteroaryl, substituted-heteroaryl, cycloalkyl, C.sub.1 -C.sub.6 alkyl, substituted-cycloalkyl, heterocycloalkyl, or substituted-heterocycloalkyl; each R.sup.5 is independently hydrogen, C.sub.1 -C.sub.6 alkyl, aryl, --(CH.sub.2).sub.n aryl, or --(CH.sub.2).sub.n cycloalkyl; each n is independently 0 to 5, m is 1 or 2, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof; and a corticosteroid, such that responsiveness of the subject to the corticosteroid is modulated as compared to when a corticosteroid alone is administered to the subject.

34. A method for modulating responsiveness to a corticosteroid in a subject, comprising: selecting a subject in need of modulation of responsiveness to a corticosteroid, wherein the subject suffers from a condition normally responsive to corticosteroid therapy; and administering to the subject an interleukin-1.beta. converting enzyme (ICE) inhibitor compound having The structure of Formula I: ##STR7## wherein R.sup.1 is hydrogen, C.sub.1 -C.sub.6 alkyl, or benzyl; R.sup.2 is --CHO, --COR.sup.a, or --CN; each R.sup.a is independently hydrogen or C.sub.1 -C.sub.6 alkyl; X is a bond, CH.sub.2, CHR.sup.5, NH, NR.sup.5, or O; R.sup.3 is aryl, substituted-aryl, heteroaryl, substituted-heteroaryl, cycloalkyl, substituted-cycloalkyl, heterocycle, or substituted-heterocycle; Y is absent, NR.sup.5, CO, S, O, SO.sub.2, --O(CHR.sup.5).sub.n --, CHR5, NR.sup.5 CO, NC(O)R.sup.5, CONR.sup.5, OCHR.sup.5, CHR.sup.5 O, SCHR.sup.5, CHR.sup.5 S, SO.sub.2 NR.sup.5, C.sub.1 -C.sub.6 alkyl, NR.sup.5 SO.sub.2, CH.sub.2 CHR.sup.5, CHR.sup.5 CH.sub.2, COCH.sub.2, or CH.sub.2 CO; R.sup.4 is absent, aryl, substituted-aryl, C.sub.1 -C.sub.8 alkyl, heteroaryl, substituted-heteroaryl, cycloalkyl, C.sub.1 -C.sub.6 alkyl, substituted-cycloalkyl, heterocycloalkyl, or substituted-heterocycloalkyl; each R.sup.5 is independently hydrogen, C.sub.1 -C.sub.6 alkyl, aryl, --(CH.sub.2).sub.n aryl, or --(CH.sub.2).sub.n cycloalkyl; each n is independently 0 to 5, m is 1 or 2, and the pharmaceutically acceptable salts, esters, amides, and prodrugs thereof, the compound being administered at a dosage and by a route sufficient to inhibit production of IFN-.gamma. in the subject, such that responsiveness of the subject to a corticosteroid is modulated as compared to when a corticosteroid alone is administered to the subject.

35. A method of claim 9, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of pemphigus vulgaris, dermatitis, atopic dermatitis, eczematous dermatitis, psoriasis, alopecia areata, allergic responses due to arthropod bite reactions, cutaneous lupus erythematosus, scleroderma, vaginitis, drug eruptions, Stevens-Johnson syndrome, leprosy reversal reactions, and erythema nodosum leprosum.

36. A method of claim 9, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of **multiple sclerosis**, autoimmune arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, autoimmune meningitis, myasthenia gravis and allergic encephalomyelitis.

37. A method of claim 9, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of systemic lupus erythematosus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, insulin-dependent diabetes mellitus, aphthous ulcer, proctitis, Wegener's granulomatosis, chronic active hepatitis, and primary biliary cirrhosis.

38. A method of claim 9, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of iritis, conjunctivitis, keratoconjunctivitis, autoimmune uveitis, Graves ophthalmopathy, and uveitis posterior.

39. A method of claim 9, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of idiopathic thrombocytopenic purpura, autoimmune thyroiditis, Sjogren's Syndrome, keratoconjunctivitis sicca secondary to

Sjogren's Syndrome, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, and polychondritis.

40. The method of claim 9, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of asthma, adult respiratory distress syndrome, inflammatory pulmonary syndrome, and interstitial lung fibrosis.

41. A method of claim 22, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of pemphigus vulgaris, dermatitis, atopic dermatitis, eczematous dermatitis, psoriasis, alopecia areata, allergic responses due to arthropod bite reactions, cutaneous lupus erythematosus, scleroderma, vaginitis, drug eruptions, Stevens-Johnson syndrome, leprosy reversal reactions, and erythema nodosum leprosum.

42. A method of claim 22, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of mutiple sclerosis, autoimmune arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis, autoimmune meningitis, myasthenia gravis and allergic encephalomyelitis.

43. A method of claim 22, wherein the subject is suffering from an innumoinflammatory disease or disorder selected from the group consisting of systemic lupus erythematosus, inflammatory bowel disease, Crohn's disease, ulcerative colitis, insulin-dependent diabetes mellitus, aphthous ulcer, procitis, Wegener's granulomatosis, chronic active hepatitis, and primary biliary cirrhosis.

44. A method of claim 22, wherein the subject is suffering from an inflammatory disease or disorder selected from the group consisting of ireitis, conjunctivitis, keratoconjunctivitis, autoimmune eveitis, Graves ophthalmopathy, and uveitis posterior.

45. A method of claim 22, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisiting of idiopathic thrombocytopenic purpura, autoimmune thyroiditis, Sjogren's Syndrome, keratoconjunctivitis sicca secondary to
Sjogren's Syndrome, aplastic anemia, pure red cell anemia, idiopathic thrombocytopenia, and polychondritis.

46. The method of claim 22, wherein the subject is suffering from an immunoinflammatory disease or disorder selected from the group consisting of asthma, adult respiratory distress syndrome, inflammatory pulmonary syndrome, and interstitial lung fibrosis.

L13 ANSWER 22 OF 32 USPATFULL
CLM What is claimed is:
1. A combination of human **IL-12** receptor specific immunoglobulins which is capable of inhibiting the binding of human **IL-12** to the high affinity human **IL-12** receptor and is capable of neutralizing human **IL-12** bioactivity by binding to the human **IL-12** receptor, wherein each individual immunoglobulin is not individually capable of inhibiting the binding of human **IL-12** to the high affinity human **IL-12** receptor.

=> d his

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     (FILE 'HOME' ENTERED AT 16:43:26 ON 21 AUG 2001)

     FILE 'EMBASE, MEDLINE, BIOSIS, USPATFULL, JAPIO, WPIDS, CAPLUS,
AGRICOLA,
     LIFESCI, BIOTECHDS, JICST-EPLUS' ENTERED AT 16:43:33 ON 21 AUG 2001
                E LEONARD JOHN/AU
L1           94 S E3
                E GOLDMAN SAMUEL/AU
L2           78 S E1-E9
                E OHARA RICHARD/AU
                E O HARA RICHARD/AU
L3           25 S E3-E7
L4          195 S L1-L3
L5            7 S L4 AND MULTIPLE SCLEROSIS
L6            6 DUP REM L5 (1 DUPLICATE REMOVED)
L7           27 S L4 AND (IL-12 OR INTERLEUKIN 12 OR INTERLUKIN)
L8            9 S L7 AND (ANTAGONIST OR ANTIBODY OR ANTIBOD?)
L9            7 DUP REM L8 (2 DUPLICATES REMOVED)
L10         609 S IL-12 AND MULTIPLE SCLEROSIS
L11         303 S L10 AND (ANTAGONIST OR ANTIBOD?)
L12          51 S L11 AND IL-12 ANTIBOD?
L13          32 DUP REM L12 (19 DUPLICATES REMOVED)

=> s il-12 and autoimmune disease

L14         610 IL-12 AND AUTOIMMUNE DISEASE

=> s l14 and (antibod? or antagonist)

L15         293 L14 AND (ANTIBOD? OR ANTAGONIST)

=> s l15 and il-12 antibod?

L16          35 L15 AND IL-12 ANTIBOD?

=> dup rem l16

PROCESSING COMPLETED FOR L16
L17          19 DUP REM L16 (16 DUPLICATES REMOVED)

=> d bib ab 1-19


L17  ANSWER 1 OF 19  USPATFULL
AN     2001:108030  USPATFULL
TI     Inhibitors of Interleukin-1.beta. converting enzyme
IN     Batchelor, Mark James, Cumnor Hill, United Kingdom
       Bebbington, David, Pewsey, United Kingdom
       Bemis, Guy W., Arlington, MA, United States
       Fridman, Wolf Herman, Paris, France
       Gillespie, Roger John, Oaksey, United Kingdom
       Golec, Julian M. C., Ashbury, United Kingdom
       Gu, Yong, Brookline, MA, United States
       Lauffer, David J., Stow, MA, United States
       Livingston, David J., Newtonville, MA, United States
       Matharu, Saroop Singh, Cricklade, United Kingdom
       Mullican, Michael D., Needham, MA, United States
       Murcko, Mark A., Holliston, MA, United States
       Murdoch, Robert, Highworth, United Kingdom
       Nyce, Philip, Milbury, MA, United States
       Robidoux, Andrea L. C., Andover, MA, United States
       Su, Michael, Newton, MA, United States
       Wannamaker, M. Woods, Stow, MA, United States
       Wilson, Keith P., Hopkinton, MA, United States
       Zelle, Robert E., Stow, MA, United States
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PA Vertex Pharmaceuticals, Incorporated, Cambridge, MA, United States (U.S. corporation)
PI US 6258948 B1 20010710
AI US 1999-400639 19990921 (9)
RLI Division of Ser. No. US 1996-761483, filed on 6 Dec 1996 Continuation-in-part of Ser. No. US 1996-712878, filed on 12 Sep 1996, now patented, Pat. No. US 5985863 Continuation-in-part of Ser. No. US 1996-598332, filed on 8 Feb 1996, now patented, Pat. No. US 5874424 Continuation-in-part of Ser. No. US 1995-575641, filed on 20 Dec 1995, now patented, Pat. No. US 6008217
PRAI US 1996-31495 19961126 (60)
DT Utility
FS GRANTED
EXNAM Primary Examiner: Kifle, Bruck
LREP Fish & Neave, Haley, Jr., Esq., James F., Joslyn, Kristin M.
CLMN Number of Claims: 46
ECL Exemplary Claim: 1
DRWN 21 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 13229
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to novel classes of compounds which are inhibitors of interleukin-IB converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently, may be advantageously used as agents against IL-1-, apoptosis-, IGIF-, and IFN-.gamma.-mediated diseases, inflammatory diseases, autoimmune diseases, destructive bone disorders, proliferative disorders, infectious diseases, degenerative diseases, and necrotic diseases. This invention also relates to methods for inhibiting ICE activity, for treating interleukin-1-, apoptosis-, IGIF- and IFN-.gamma.-mediated diseases and decreasing IGIF and IFN-.gamma. production using the compounds and compositions of this invention. This invention also relates to methods for preparing N-acylamino compounds.

L17 ANSWER 2 OF 19 USPATFULL
AN 2001:107647 USPATFULL
TI Human **antibodies** that bind human TNF.alpha.
IN Salfeld, Jochen G., North Grafton, MA, United States
Allen, Deborah J., Cambridge, United Kingdom
Hoogenboom, Hendricus R. J. M., Hertogsingel, MA, United States
Kaymakcalan, Zehra, Westboro, MA, United States
Labkovsky, Boris, Framingham, MA, United States
Mankovich, John A., Andover, MA, United States
McGuinness, Brian T., Comberton, United Kingdom
Roberts, Andrew J., Cambridge, United Kingdom
Sakorafas, Paul, Newton, MA, United States
Schoenhaut, David, Garfield, NJ, United States
Vaughan, Tristan J., Impington, United Kingdom
White, Michael, Framingham, MA, United States
Wilton, Alison J., Cambridge, United Kingdom
PA BASF Aktiengesellschaft, Rheiland-Pfalz, Germany, Federal Republic of (non-U.S. corporation)
PI US 6258562 B1 20010710
WO 9729131 19970814
AI US 1999-125098 19990316 (9)
WO 1997-US2219 19970210
19990316 PCT 371 date
19990316 PCT 102(e) date
RLI Continuation-in-part of Ser. No. US 1996-599226, filed on 9 Feb 1996, now patented, Pat. No. US 6090382
PRAI US 1996-31476 19961125 (60)

DT Utility
FS GRANTED
EXNAM Primary Examiner: Saunders, David
LREP Lahive & Cockfield, LLP, DeConti, Jr., Giulio A., Hanley, Elizabeth A.
CLMN Number of Claims: 20
ECL Exemplary Claim: 1
DRWN 10 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 2754
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Human **antibodies**, preferably recombinant human **antibodies**, that specifically bind to human tumor necrosis factor .alpha.(hTNF.alpha.) are disclosed. These **antibodies** have high affinity for hTNF.alpha. (e.g., K.sub.d =10.sup.-8 M or less), a slow off rate for hTNF.alpha. dissociation (e.g., K.sub.off =10.sup.-3 sec.sup.-1 or less) and neutralize hTNF.alpha. activity in vitro and in vivo. An **antibody** of the invention can be a full-length **antibody** or an antigen-binding portion thereof. The **antibodies**, or **antibody** portions, of the invention are useful for detecting hTNF.alpha. and for inhibiting hTNF.alpha. activity, e.g., in a human subject suffering from a disorder in which hTNF.alpha. activity is detrimental. Nucleic acids, vectors and host cells for expressing the recombinant human **antibodies** of the invention, and methods of synthesizing the recombinant human **antibodies**, are also encompassed by the invention.

L17 ANSWER 3 OF 19 USPATFULL
AN 2001:52062 USPATFULL
TI Thienodipyridine derivatives, production and use thereof
IN Sohda, Takashi, Takatsuki, Japan
Makino, Haruhiko, Hyogo, Japan
Baba, Atsuo, Ashiya, Japan
Yamane, Taihei, Ikeda, Japan
PA Takeda Chemical Industries, Ltd., Osaka, Japan (non-U.S. corporation)
PI US 6214838 B1 20010410
WO 9965916 19991223
AI US 1999-355218 19990723 (9)
WO 1999-JP3155 19990614
19990723 PCT 371 date
19990723 PCT 102(e) date
PRAI JP 1998-166910 19980615
DT Utility
FS Granted
EXNAM Primary Examiner: Huang, Evelyn Mei
LREP Riesen, Philippe Y., Chao, Mark
CLMN Number of Claims: 33
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 1733
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB A compound of the formula (I): ##STR1##

wherein R is hydrogen or C.sub.2-6 alkanoyl; X is halogen; and ring A is benzene ring which is optionally substituted by 1 to 4 substituents selected from 1 halogen, 2 hydroxy, 3 C.sub.1-6 alkoxy optionally substituted by halogen or phenyl, 4 C.sub.1-6 alkylthio optionally substituted by halogen or phenyl, 5 C.sub.1-6 alkyl optionally substituted by halogen, 6 C.sub.2-6 alkanoylamino or 7 carboxy optionally esterified by C.sub.1-6 alkyl, or a salt thereof; which can be used for preventing or treating inflammatory disease, arthritis, chronic rheumatoid arthritis, autoimmune diseases, or rejection after organ transplantation.

L17 ANSWER 4 OF 19 USPATFULL
AN 2001:40475 USPATFULL
TI Inhibitors of interleukin-1.beta. Converting enzyme inhibitors
IN Batchelor, Mark James, Cumnor Hill, United Kingdom
Bebbington, David, Pewsey, United Kingdom
Bemis, Guy W., Arlington, MA, United States
Fridman, Wolf Herman, Paris, France
Gillespie, Roger John, Malmesbury, United Kingdom
Golec, Julian M. C., Swindon, United Kingdom
Gu, Yong, Brookline, MA, United States
Lauffer, David J., Stow, MA, United States
Livingston, David J., Newtonville, MA, United States
Matharu, Saroop Singh, Cricklade, United Kingdom
Mullican, Michael D., Needham, MA, United States
Murcko, Mark A., Holliston, MA, United States
Murdoch, Robert, Highworth, United Kingdom
Nyce, Philip, Milbury, MA, United States
Robidoux, Andrea L. C., Andover, MA, United States
Su, Michael, Newton, MA, United States
Wannamaker, M. Woods, Stow, MA, United States
Wilson, Keith P., Hopkinton, MA, United States
Zelle, Robert E., Stow, MA, United States
PA Vertex Pharmaceuticals Incorporated, Cambridge, MA, United States (U.S. corporation)
PI US 6204261 B1 20010320
AI US 1996-761483 19961206 (8)
RLI Continuation-in-part of Ser. No. US 1996-712878, filed on 12 Sep 1996 Continuation-in-part of Ser. No. US 1996-598332, filed on 8 Feb 1996, now patented, Pat. No. US 5874424 Continuation-in-part of Ser. No. US 1995-575641, filed on 20 Dec 1995
PRAI US 1996-31495 19961126 (60)
DT Utility
FS Granted
EXNAM Primary Examiner: Gupta, Yogendra N.; Assistant Examiner: Kifle, Bruck
LREP Fish & Neave, Haley, Jr., James F., Dixon, Lisa A.
CLMN Number of Claims: 34
ECL Exemplary Claim: 1
DRWN 20 Drawing Figure(s); 11 Drawing Page(s)
LN.CNT 12975
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to pyradazino[1,2-a][1,2]diazepine-1-carboxamide compounds of formula: ##STR1##

which compounds are inhibitors of interleukin-1beta converting enzyme.

L17 ANSWER 5 OF 19 USPATFULL
AN 2000:80750 USPATFULL
TI Substituted benzamides
IN Germann, Tieno, Herzogenrath, Germany, Federal Republic of
Frosch, Stefanie, Aachen, Germany, Federal Republic of
Zimmer, Oswald, Wuerselen, Germany, Federal Republic of
PA Gruenenthal GmbH, Aachen, Germany, Federal Republic of (non-U.S. corporation)
PI US 6080742 20000627
AI US 1999-405180 19990924 (9)
PRAI DE 1998-19843793 19980924
DT Utility
FS Granted
EXNAM Primary Examiner: Stockton, Laura L.
LREP Evenson, McKeown, Edwards & Lenahan, P.L.L.C.
CLMN Number of Claims: 4
ECL Exemplary Claim: 1
DRWN No Drawings
LN.CNT 426
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB Substituted benzamides corresponding to the formula I ##STR1## wherein R.sup.1, R.sup.2 and R.sup.3 have the meanings given herein, and their use in pharmaceutical compositions. The compounds are particularly useful as immunomodulators.

L17 ANSWER 6 OF 19 USPATFULL
AN 2000:50737 USPATFULL
TI Methods and compositions for modulating responsiveness to corticosteroids
IN Sekut, Les, Westborough, MA, United States
Carter, Adam, Newburyport, MA, United States
Ghayur, Tariq, Grafton, MA, United States
Banerjee, Subhashis, Shrewsbury, MA, United States
Tracey, Daniel E., Harvard, MA, United States
PA BASF Aktiengesellschaft, Rheinland Pfalz, Germany, Federal Republic of (non-U.S. corporation)
PI US 6054487 20000425
AI US 1997-820692 19970318 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Jarvis, William R. A.
LREP Lahive & Cockfield, LLP
CLMN Number of Claims: 46
ECL Exemplary Claim: 1
DRWN 3 Drawing Figure(s); 3 Drawing Page(s)
LN.CNT 2404
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Method for modulating responsiveness to corticosteroids in a subject are provided. In the method of the invention, an agent which antagonizes a factor that regulates production of IFN-.gamma. in the subject is administered to the subject in combination with a corticosteroid such that responsiveness of the subject to the corticosteroid is modulated as compared to when a corticosteroid alone is administered to the subject. In one embodiment, the agent is an interferon-.gamma. inducing factor (IGIF) **antagonist**. In another embodiment, the agent is an interleukin-12 (**IL-12**) **antagonist**. In a preferred embodiment, the agent is an inhibitor of a caspase family protease, preferably an ICE inhibitor. In another preferred embodiment, the agent is an anti-**IL-12** monoclonal **antibody**. Other preferred agents include phosphodiesterase IV inhibitors and beta-2 agonists. The methods of the invention can be used in the treatment of a variety of inflammatory and immunological diseases and disorders. Pharmaceutical compositions comprising an agent which antagonizes a factor that regulates production of IFN-.gamma. in a subject, a corticosteroid and a pharmaceutically acceptable carrier are also provided. A preferred composition comprises an ICE inhibitor, a corticosteroid and a pharmaceutically acceptable carrier.

L17 ANSWER 7 OF 19 USPATFULL
AN 2000:4432 USPATFULL
TI Methods for enhancement of protective immune responses
IN Reed, Steven G., Bellevue, WA, United States
PA Corixa Corporation, Seattle, WA, United States (U.S. corporation)
PI US 6013268 20000111
AI US 1997-989370 19971212 (8)
RLI Continuation-in-part of Ser. No. US 1996-634642, filed on 18 Apr 1996, now patented, Pat. No. US 5879687, issued on 9 Mar 1999 which is a continuation-in-part of Ser. No. US 1996-607509, filed on 23 Feb 1996, now patented, Pat. No. US 5876735, issued on 2 Mar 1999 which is a continuation-in-part of Ser. No. US 1995-488386, filed on 6 Jun 1995, now abandoned which is a continuation-in-part of Ser. No. US

1995-454036, filed on 30 May 1995, now patented, Pat. No. US 5876966, issued on 2 Mar 1999 which is a continuation-in-part of Ser. No. US 1994-232534, filed on 22 Apr 1994, now abandoned
DT Utility
FS Granted
EXNAM Primary Examiner: Minnifield, Nita
LREP Seed & Berry LLP
CLMN Number of Claims: 9
ECL Exemplary Claim: 1
DRWN 33 Drawing Figure(s); 30 Drawing Page(s)
LN.CNT 2882
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB Methods for eliciting or enhancing immune responses to antigens, including tumor antigens, and/or DNA vaccines are provided. The methods employ polypeptides or nucleic acid compositions that contain at least a biologically active portion of a Leishmania braziliensis or Leishmania major homologue of the eukaryotic initiation factor 4A, or a variant thereof. Such polypeptides and compositions are useful for enhancing or eliciting a patient's cellular and/or humoral immune response, for instance within methods for treating tumors.

L17 ANSWER 8 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000426141 EMBASE
TI Suppression and acceleration of autoimmune diabetes by neutralization of endogenous interleukin-12 in NOD mice.
AU Fujihira K.; Nagata M.; Moriyama H.; Yasuda H.; Arisawa K.; Nakayama M.; Maeda S.; Kasuga M.; Okumura K.; Yagita H.; Yokono K.
CS M. Nagata, Department of Geriatric Medicine, Kobe University School of Medicine, 7-5-1 Kusunokicho, Chuo-ku, Kobe 650-0017, Japan. nagata@med.kobe-u.ac.jp
SO Diabetes, (2000) 49/12 (1998-2006).
Refs: 55
ISSN: 0012-1797 CODEN: DIAEAZ
CY United States
DT Journal; Article
FS 003 Endocrinology
026 Immunology, Serology and Transplantation
LA English
SL English
AB A corpus of evidence suggests that T-helper type 1 (Th1)-dependent cellular immunity plays a pivotal role in the pathogenesis of autoimmune diabetes. This study was intended to find ways to prevent the development of NOD diabetes using a neutralizing anti-interleukin (**IL**)-**12 antibody** (C17.8) that inhibits Th1 cell differentiation. When C17.8 was administered from 5 to 30 weeks of age, NOD mice exhibited sup- i pression of both insulitis and diabetes. However, when C17.8 administration ceased at 15 weeks of age, 8 of 13 recipients showed diabetes at 30 weeks of age. These results suggest that **IL-12** plays an important role not only in the development of effector cells but also in their activation. In contrast, when C17.8 was injected into 2-week-old female NOD mice for 6 consecutive days, all 16 recipients showed diabetes at 30 weeks of age, whereas 12 of 20 control mice became diabetic. This result suggests that depletion of endogenous **IL-12** at a young age results in the enhancement of diabetes. Flow cytometric analysis indicated that i activated memory T-cells were present in higher numbers after C17.8 treatment. Transfer of spleen i cells from 15-week-old C17.8-treated NOD mice to NOD-scid mice resulted in an earlier onset and a higher incidence of diabetes. Furthermore, administration of C17.8 to 2-week-old NOD mice also resulted in a much earlier onset of diabetes. These results suggest that short-term treatment with anti-**IL-12 antibody** prohibits IL-2 production at a young age, which may influence the expansion and apoptosis of pathogenic T-cells, resulting in the acceleration of autoimmune diabetes.

L17 ANSWER 9 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000350841 EMBASE
TI Murine concanavalin A-induced hepatitis is prevented by interleukin 12 (**IL-12**) **antibody** and exacerbated by exogenous **IL-12** through an interferon-.gamma.-dependent mechanism.
AU Nicoletti F.; Di Marco R.; Zaccone P.; Salvaggio A.; Magro G.; Bendtzen K.; Meroni P.
CS Dr. F. Nicoletti, Via Luigi Sturzo n.3, 95021 Cannizzaro, Catania, Italy. ferdinic@ctonline.it
SO Hepatology, (2000) 32/4 I (728-733).
Refs: 53
ISSN: 0270-9139 CODEN: HPTLD
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
037 Drug Literature Index
048 Gastroenterology
LA English
SL English
AB Concanavalin A (ConA)-induced hepatitis is a cell-mediated immunoinflammatory condition similar to human autoimmune hepatitis. We investigated the role of interleukin 12 (**IL-12**) in hepatitis induced in NMRI and C57/BL6 mice by a single injection of ConA. Recombinant murine **IL-12** administered 24 hours and 1 hour prior to ConA exacerbated both transaminase activities in plasma and histologic signs of hepatitis. These markers of liver injury were significantly reduced by prophylactic, but not therapeutic treatment with anti-**IL-12** monoclonal **antibody** (mAb). The disease-modulatory effects of **IL-12** and anti-**IL-12** mAb were associated with profound and reverse modifications of a ConA-induced increase in the circulating levels of IL-4, IL-6, interferon gamma (IFN-.gamma.) and tumor necrosis factor (TNF). Relative to control animals receiving ConA alone, the plasma levels of these cytokines were all augmented in **IL-12** /ConA-treated mice and diminished in anti-**IL-12** mAb/ConA-treated mice. Anti-IFN-.gamma. mAb also impeded the appearance of **IL-12**/ConA-induced hepatitis. Thus, **IL-12**-induced production of IFN-.gamma. might play a role in mediating the hepatitis-inducing effect of ConA. However, IL-12p40-deficient C57/BL6 mice were as susceptible as wild-type controls to the hepatitis-inducing effect of ConA.

L17 ANSWER 10 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.
AN 2000153043 EMBASE
TI Anti-interleukin-12 **antibody**: Potential role in preventing relapses of multiple sclerosis.
AU Fox R.J.; Rostami A.M.
CS Dr. A.M. Rostami, Department of Neurology, Univ. of Pennsylvania Medical Center, 3400 Spruce Street, Philadelphia, PA 19104-4283, United States. rostamia@mail.med.upenn.edu
SO BioDrugs, (2000) 13/4 (233-241).
Refs: 71
ISSN: 1173-8804 CODEN: BIDRF4
CY New Zealand
DT Journal; Article
FS 008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
037 Drug Literature Index
039 Pharmacy
LA English
SL English
AB Multiple sclerosis is an inflammatory demyelinating disorder of the

central nervous system. Immunological evidence from patients with multiple sclerosis and experimental models suggests that the cytokine interleukin-12 (**IL-12**) plays an important role in the pathogenesis of inflammatory demyelination. In experimental autoimmune encephalomyelitis, an animal model of multiple sclerosis, **antibodies** that block **IL-12** can prevent relapses of the disease. Anti-**IL-12 antibodies** present a novel approach for preventing relapses in multiple sclerosis.

L17 ANSWER 11 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 1
AN 2000274868 EMBASE
TI Defective regulation of IFN.gamma. and **IL-12** by endogenous IL-10 in progressive MS.
AU Balashov K.E.; Comabella M.; Ohashi T.; Khoury S.J.; Weiner H.L.
CS Dr. H.L. Weiner, Center for Neurologic Diseases, Brigham and Women's Hospital, HIM-730, 77 Avenue Louis Pasteur, Boston, MA 02115-5817, United States. weiner@cnd.bwh.harvard.edu
SO Neurology, (2000) 55/2 (192-198).
Refs: 34
ISSN: 0028-3878 CODEN: NEURAI
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LA English
SL English
AB Background: MS is a chronic inflammatory disease of the CNS postulated to be a Th1 type cell-mediated **autoimmune disease**. There is increased interferon-.gamma. (IFN.gamma.) secretion in MS, and IFN.gamma. administration induces exacerbations of disease. IFN.gamma. expression is closely regulated by a number of cytokines produced by different cells of the immune system. Interleukin-12 (**IL-12**) is a major factor leading to Th1-type responses, including IFN.gamma. secretion, and there is increased secretion of **IL-12** in MS. IL-10 is a potent inhibitor of both **IL-12** and IFN.gamma. expression. Methods: The authors investigated cytokine production and proliferative responses of peripheral blood mononuclear cells stimulated with soluble anti-CD3 in healthy controls and patients with stable relapsing-remitting MS or progressive MS. Results: The authors found that T cell receptor-mediated IFN.gamma. and IL-10 secretion were increased in progressive MS, whereas IL-4 and IL-2 secretion and lymphocyte proliferative responses were normal. Anti-**IL-12 antibody** suppressed raised IFN.gamma. in progressive MS but did not affect raised IL-10. In addition, neutralization of endogenous IL-10 upregulated IFN.gamma. in controls but not progressive MS. IL-10 was produced by CD4+ cells whereas IFN.gamma. was produced by both CD4+ and CD8+ cells. There were no differences in IL-10 receptor expression in MS patients. Conclusions: These abnormalities in IL-10 regulation were not seen in the relapsing-remitting form of MS. Thus, the defect in regulation of both **IL-12** and IFN.gamma. production by endogenous IL-10 in progressive MS could be an important factor involved in the transition of MS from the relapsing to the progressive stage and has implications for treating MS patients with exogenous IL-10.

L17 ANSWER 12 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1999:487326 CAPLUS
DN 131:129052
TI **Antibodies** against human **IL-12**
IN Gately, Maurcie Kent; Presky, David Howard
PA F.Hoffmann-La Roche A.-G., Switz.

SO PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9937682	A2	19990729	WO 1999-EP202	19990115
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9925177	A1	19990115	AU 1999-25177	19990115
BR 9907743	A	20001017	BR 1999-7743	19990115
EP 1049717	A2	20001108	EP 1999-904780	19990115
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
US 6225117	B1	20010501	US 1999-232522	19990119
PRAI US 1998-72333	P	19980123		
WO 1999-EP202	W	19990115		

AB The present invention relates to p75 heterodimer specific anti-human **IL-12 antibodies** that are characterized by a higher potency and greater efficacy in neutralizing human **IL-12** bioactivity than known heterodimer specific **IL-12** monoclonal **antibodies**. The heterodimer specific **antibodies** recognize one or more epitopes of the human **IL-12** p75 heterodimer, but do not bind to the p40 subunit alone. The heterodimer specific **IL-12 antibodies** neutralize rhesus monkey **IL-12** bioactivity with a potency similar to their potency for neutralizing human **IL-12** bioactivity making them useful **IL-12** antagonists. The monoclonal **antibodies** are therefore useful for diseases assocd. with aberrant Th1-type helper cell activity, e.g. multiple sclerosis, rheumatoid arthritis, autoimmune diabetes mellitus, Crohn's disease and ulcerative colitis.

L17 ANSWER 13 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 2
AN 1999267907 EMBASE
TI **IL-12** as a therapeutic target for pharmacological modulation in immune-mediated and inflammatory diseases: Regulation of T helper 1/T helper 2 responses.
AU Hasko G.; Szabo C.
CS G. Hasko, Inotek Corp, 100 Cummings Center, Beverly, Massachusetts, MA 01915, United States. ghasko@inotekcorp.com
SO British Journal of Pharmacology, (1999) 127/6 (1295-1304).
Refs: 129
ISSN: 0007-1188 CODEN: BJPCBM
CY United Kingdom
DT Journal; General Review
FS 026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB 1. Interleukin-12 (**IL-12**) is a pivotal cytokine in driving the immune system towards a T helper (Th)1 type response and preventing a Th2 type immune profile. Therefore, **IL-12** is indispensable in the defense against certain, mainly intracellular pathogens, but overproduction of this cytokine is crucially involved in the etiology of several inflammatory and autoimmune diseases. 2. Hence, **IL-12** is an ideal target for pharmacological

intervention in the therapy of autoimmune and inflammatory diseases. 3. The production of **IL-12** and a resultant Th1 type immune response can be suppressed with several pharmacological approaches including modulation of intracellular cyclic AMP levels, glucocorticoids and nuclear factor-.kappa.B inhibition. **IL-12** responsiveness may be inhibited using anti-**IL-12** **antibodies**, soluble **IL-12** receptors or the **IL-12** p46 homodimer. 4. Exploitation of these approaches may provide novel means for the experimental therapy of a variety of pathophysiological states.

L17 ANSWER 14 OF 19 USPATFULL
AN 1998:161997 USPATFULL
TI **Antibody** to interleukin-12 receptor
IN Gately, Maurice Kent, Pine Brook, NJ, United States
Presky, David Howard, Glen Ridge, NJ, United States
Wu, Chang-you, Belleville, NJ, United States
PA Hoffmann-La Roche Inc., Nutley, NJ, United States (U.S. corporation)
PI US 5853721 19981229
AI US 1995-381059 19950131 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Feisee, Lila; Assistant Examiner: Sun-Hoffman, Lin
LREP Johnston, George W., Tramaloni, Dennis P., Kass, Alan P.
CLMN Number of Claims: 1
ECL Exemplary Claim: 1
DRWN 33 Drawing Figure(s); 22 Drawing Page(s)
LN.CNT 1418
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention relates to a novel **antibody** against the **IL-12** receptor and a novel combination of anibodies anainst the **IL-12** receptor. The novel anti-**IL-12** receptor anbody, designated as 2B10, provided in accordance with the present invention binds to the human **IL-12** receptor but which is not capable of inhibiting the binding of human **IL-12** to the high affinity human **IL-12** receptor and is not capable of neutralizing human **IL-12** bioactivity by binding to human **IL-12** receptor.

L17 ANSWER 15 OF 19 CAPLUS COPYRIGHT 2001 ACS
AN 1998:251074 CAPLUS
DN 128:307519
TI Methods for enhancing oral tolerance and treating **autoimmune disease** using inhibitors of interleukin-12
IN Strober, Warren; Kelsall, Brian L.; Marth, Thomas
PA United States Dept. of Health and Human Services, USA; Strober, Warren; Kelsall, Brian L.; Marth, Thomas
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9816248	A1	19980423	WO 1996-US16007	19961011
	W: AU, CA, JP, US				
	AU 9672576	A1	19980511	AU 1996-72576	19961011
PRAI	WO 1996-US16007		19961011		

AB The present invention provides a method for enhancing oral tolerance to an antigen assocd. with an **autoimmune disease** in a subject having the **autoimmune disease** comprising orally administering to the subject an antigen assocd. with the **autoimmune disease** and administering an inhibitor of

interleukin-12 in amts. sufficient to enhance oral tolerance. Also provided in the present invention is a method for treating or preventing an **autoimmune disease** in a subject comprising orally administering to the subject an antigen assocd. with the **autoimmune disease** and administering an inhibitor of interleukin-12 in amts. sufficient to treat or prevent the **autoimmune disease**, thereby treating or preventing the **autoimmune disease**. The interleukin 12 inhibitor is an **antibody** or monoclonal **antibody**.

L17 ANSWER 16 OF 19 USPATFULL
AN 97:80900 USPATFULL
TI **IL-12** inhibition of B1 cell activity
IN Metzger, Dennis W., Sylvania, OH, United States
Van Cleave, Victor H., Londonderry, NH, United States
PA Genetics Institute, Cambridge, MA, United States (U.S. corporation)
Medical College of Ohio, Toledo, OH, United States (U.S. corporation)
PI US 5665347 19970909
AI US 1995-382658 19950202 (8)
DT Utility
FS Granted
EXNAM Primary Examiner: Achutamurthy, Ponnathapura
LREP Hamilton, Brook, Smith & Reynolds, P.C.
CLMN Number of Claims: 7
ECL Exemplary Claim: 1,2
DRWN 47 Drawing Figure(s); 18 Drawing Page(s)
LN.CNT 942
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The invention relates to a method of suppressing B1 cell activity in a host (e.g., mammalian, including human) comprising administering to the host an effective amount of **IL-12** that significantly suppresses or inhibits B1 cell activity. In addition, the invention relates to a method of treating a B1 cell disorder in a host, comprising administering to the host an effective therapeutic amount of **IL-12**. The invention further encompasses a method of screening for substances (e.g., proteins, peptides, small molecules) which enhance or suppress the inhibition of B1 cell activity by **IL-12**. The invention also relates to a substance identified by the methods of screening for a substance which enhances or suppresses **IL-12** inhibition of B1 cell activity.

L17 ANSWER 17 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 3
AN 97036980 EMBASE
DN 1997036980
TI Increased interleukin 12 production in progressive multiple sclerosis: Induction by activated CD4+ T cells via CD40 ligand.
AU Balashov K.E.; Smith D.R.; Khoury S.J.; Hafler D.A.; Weiner H.L.
CS H.L. Weiner, Center for Neurologic Diseases, Brigham and Women's Hospital, 221 Longwood Avenue, Boston, MA 02115, United States. weiner@cnd.bwh.harvard.edu
SO Proceedings of the National Academy of Sciences of the United States of America, (1997) 94/2 (599-603).
Refs: 33
ISSN: 0027-8424 CODEN: PNASA6
CY United States
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
008 Neurology and Neurosurgery
026 Immunology, Serology and Transplantation
LA English
SL English
AB Multiple sclerosis (MS) is a chronic inflammatory disease of the central

nervous system postulated to be a cell-mediated **autoimmune disease** in which interferon .gamma. (IFN-.gamma.) plays an important role. There is increased IFN-.gamma. secretion in MS, and IFN-.gamma. administration induces exacerbations of disease. We found that interleukin 12 (**IL-12**) was responsible for raised IFN-.gamma. secretion in MS as anti-**IL-12** **antibodies** reversed raised anti-CD3-induced IFN-.gamma. in MS patients to normal levels. Furthermore, we found a marked increase in T cell receptor-mediated **IL-12** secretion in progressive MS patients vs. controls (24.8 .+-. 7.7 pg/ml vs. 1.5 .+-. 1.0 pg/ml, P = 0.003) and vs. relapsing-remitting patients (3.7 .+-. 1.4 pg/ml, P < 0.05). Investigation of the cellular basis for raised **IL-12** demonstrated that T cells from MS patients induced **IL - 12** secretion from non-T cells, and that T cells from MS patients could even drive non-T cells from normal subjects to produce increased **IL-12**. Anti-CD40 ligand **antibody** completely blocked **IL-12** secretion induced by activated T cells, and we found increased CD40 ligand expression by activated CD4+ T cells in MS patients vs. controls. The CD40 ligand-dependent Th1-type immune activation was observed in the progressive but not in the relapsing-remitting form of MS, suggesting a link to disease pathogenesis and progression and providing a basis for immune intervention in the disease.

L17 ANSWER 18 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 4
AN 96137575 EMBASE
DN 1996137575
TI The role of interleukin 12 and nitric oxide in the development of spontaneous **autoimmune disease** in MRL/MP-lpr/lpr mice.
AU Huang F.-P.; Feng G.-J.; Lindop G.; Stott D.I.; Liew F.Y.
CS Department of Immunology, Western Infirmary, University of Glasgow,Glasgow G11 6NT, United Kingdom
SO Journal of Experimental Medicine, (1996) 183/4 (1447-1459). ISSN: 0022-1007 CODEN: JEMEAV
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB MRL/MP-lpr/lpr (MRL/lpr) mice develop a spontaneous **autoimmune disease**. Serum from these mice contained significantly higher concentrations of nitrite/nitrate than serum from age-matched control MRL/MP-+/+ (MRL/+), BALB/c or CBA/6J mice. Spleen and peritoneal cells from MRL/lpr mice also produced significantly more nitric oxide (NO) than those from the control mice when cultured with interferon (IFN) .gamma. and lipopolysaccharide (LPS) in vitro. It is interesting to note that peritoneal cells from MRL/lpr mice also produced markedly higher concentrations of interleukin (**IL**) **12** than those from MRL/+ or BALB/c mice when cultured with the same stimuli. It is striking that cells from MRL/lpr mice produced high concentrations of NO witch cultured with **IL-12** and IPS, whereas only low or background levels of NO were produced by similarly cultured cells from MRL/+ or BALB/c mice. The enhanced NO synthesis induced by IFN-.gamma./LPS was substantially inhibited by anti-**IL-12** **antibody**. In addition, **IL-12**-induced NO production can also be markedly inhibited by anti-IFN-.gamma. **antibody**, but only weakly inhibited by anti-tumor necrosis factor .alpha. **antibody**. The effect of **IL-12** on NO production was dependent on the presence of natural killer and possibly T cells. Serum from MRL/lpr mice contained significantly higher concentrations of **IL-12** compared with those of MRL/+

or BALB/c control mice. Daily injection of recombinant **IL-12** led to increased serum levels of IFN-.gamma. and NO metabolites, and accelerated glomerulonephritis in the young MRL/lpr mice (but not in the MRL/+ mice) compared with controls injected with phosphate-buffered saline alone. These data, together with previous finding that NO synthase inhibitors can ameliorate **autoimmune disease** in MRL/lpr mice, suggest that the high capacity of such mice to produce **IL-12** and their greater responsiveness to **IL-12**, leading to the production of high concentrations of NO, are important factors in this spontaneous model of **autoimmune disease**.

L17 ANSWER 19 OF 19 EMBASE COPYRIGHT 2001 ELSEVIER SCI. B.V.DUPLICATE 5
AN 96165859 EMBASE
DN 1996165859
TI **IL-12** inhibits endotoxin-induced inflammation in the eye.
AU Whitcup S.M.; Rizzo L.V.; Lai J.C.; Hayashi S.; Gazzinelli R.; Chan C.-C.
CS National Eye Institute, 10 Center Drive,Bethesda, MD 20892-1858, United States
SO European Journal of Immunology, (1996) 26/5 (995-999).
ISSN: 0014-2980 CODEN: EJIMAF
CY Germany
DT Journal; Article
FS 012 Ophthalmology
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB Interleukin-12 (**IL-12**) is a heterodimeric cytokine that induces interferon (IFN)-.gamma., production and an increased generation of Th1 cells. Both **IL-12** and **IL-12** antagonists are being studied for the treatment of allergic reactions, **autoimmune disease** and malignancy. The goal of the present experiments was to examine the importance of **IL-12** in endotoxin-induced ocular inflammation. The number of inflammatory cells infiltrating eyes with endotoxin-induced uveitis (EIU) was significantly increased in animals treated with intraperitoneal anti-**IL-12 antibody** when compared to control animals, but there was no difference in infiltrating inflammatory cells in the eyes of animals treated with **IL-12** when compared to controls. In contrast, intraocular injection of **IL-12** significantly inhibited the development of endotoxin-induced intraocular inflammation. The infiltrating inflammatory cells were reduced in the eyes of animals receiving intraocular **IL-12** when compared to controls. Cytokine analysis of the aqueous humor obtained from eyes with EIU showed increased levels of IFN-.gamma. and decreased levels of IL-6 in eyes receiving intraocular **IL-12**. These data show that **IL-12** has an inhibitory effect on endotoxin-induced inflammation in the eye and suggest that **IL-12** can have an immunoregulatory function in some forms of inflammatory disease.